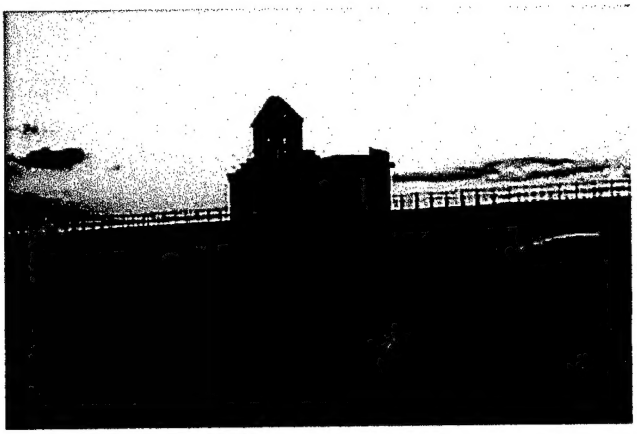
Workshop on Recent Advances in Fluorinated Surfactants



26, 27 January 2001
Université d'Avignon et des Pays de Vaucluse
France

Coordinated by :

Laboratoire de Chimie Bioorganique et des systèmes moléculaires vectoriels

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Workshop on Recent Advances in Fluorinated Surfactants

This workshop aims to explore fundamental science questions related to fluorosurfactant assemblies, including micelles, microemulsions and vesicles; fluorosurfactant solutions and self-assembly in non-aqueous media such as fluorocarbons and dense carbon dioxide; fluorosurfactants in blood substitute formulations, oxygen and drug delivery systems; and fluorosurfactants in new coatings protocols and applications in microelectronics and patterning.
Decontamination of warfare agents in a contamination event could be achieved by systems involving fluorinated surfactants.

REPORT

Workshop on

Recent Advances in Fluorinated Surfactants

Université d'Avignon et des Pays de Vaucluse
France
January 26 and 27, 2001

The workshop entitled "Recent Advances in Fluorinated Surfactants" was held in Avignon, France January 26th and 27th 2001. This event was organized by the "Laboratoire de Chimie Bioorganique et des Systèmes Moléculaires Vectoriels" at the University of Avignon", with financial support coming from the ERO.

Fluorine chemistry was initially centered on simple industrial applications such as the synthesis of polymers (teflon) or gases (freons). Nevertheless, the last two decades have seen the development of novel perfluorocarbon amphiphiles. Their outstanding chemical and thermal stability allows applications under conditions, which would be too severe for hydrocarbon amphiphiles. In addition, this type of molecule can lower the surface tension of water more than hydrocarbon-based analogues. Numerous applications of fluorinated surfactants have been developed, thus they are used in adhesive formulation, as antifogging agents, as antistatic agents, cleaning materials, cosmetics, emulsions, fire-fighting foams, herbicide formulations etc.

The workshop focused on two primary objectives:

The first one was to bring together international academic researchers working on fluorinated surfactants to stimulate creativity and collaboration among the scientists and develop new applications. The number of attendees was limited intentionally to 25 people to allow constructive discussions. Each participant presented a 30 minute seminar talk on his or her research work.

The second objective was to provide information on this unavoidable chemistry field to the ARO.

During this workshop several questions relative to fluorinated chemistry were featured and discussed:

- First, preparations of new polymers derived from hydrocarbon and fluorocarbon surfactants were described by Dr. Francoise Candau and Pr. Professeur André Laschewsky (from respectively the "Institut Charles Sadron" (Strasbourg, France) and University of Louvain La neuve (Belgium)). The possibility of synthesizing polymers made of hydrophobic microdomains of different nature and connected by hydrophilic linear spacers was underlined. Such systems could be of particular interest for the specific solubilization of mutually incompatible hydrophobic compounds.
- It is known that Fluorocarbon emulsions can provide a simple, safe and immediately effective means of delivering oxygen to tissues during surgical operations. Consequently, the synthesis of new bio-compatible fluorinated surfactants is now needed to stabilize more efficiently these emulsions. Pr. J. G. Riess from the University of California (San Diego, USA), presented the state of the art in this chemistry area which could be used for both military and civilian purposes. Fluorinated surfactants are now more than essential for preparing blood substitute.
- Fluorocarbon amphiphiles are also used to crystallize hydrophilic proteins or solubilize membrane components in aqueous media. Pr. Charles Mioskowsky (University of Strasbourg, France) demonstrated that amphiphiles bearing two hydrophobic hydro/fluorocarbon tails can induce crystallization. This process would help scientists to better understand the behavior of water soluble proteins. Dr. Jean Jacques Benattar (CEA Saclay, France) showed the potentialities of these surfactants to form Black Films and their applications to study proteins by X-ray techniques.
- The use of fluorinated surfactant in fire fighting foams was presented by Dr. Pabon (Elf-Atochem, France). Here again, films formed by these fluorinated molecules could be developed for both civilian and military applications.
- Enzymology in super-critical fluid emulsions was presented by Dr B. Robinson et Dr. J. Eastoe (University of Bristol, UK). Interestingly, it was found that fluorocarbon amphiphiles can

stabilize such emulsions and consequently could provide new tools for decontamination of chemical warfare.

- The paper on combinatorial synthesis presented by Pr. F. M. Menger (Emory University, USA) gave a new dimension to this chemistry field. New fluorinated gemini surfactants prepared following this original synthetic procedure could provide efficiently a large diversity of structures. Numerous fundamental questions were also presented by other specialists such as; Pr. A. Lattes (University of Toulouse, France), Pr. C. Selve (University of Nancy, France) or Dr. F. Guittard (University of Nice Sophia-Antipolis, France).
- Finally the ability of these molecules to form "nano-systems", vesicles, fibers was explained by Dr. M. P. Krafft (Institut Charles Sadron, Stasbourg, France). Dr. B. Ameduri (University of Montpellier, France) discussed the potentialities of new hydro-fluorocarbon polymers.

All these high quality presentations were debated in group discussions. One can note that the schedule and the organization chosen for this workshop was quite appropriate to induce deep scientific exchanges and new collaborations.

In conclusion, this meeting underlined mainly the potential applications of highly fluorinated molecules in the following areas; decontamination, medicine, biology... Furthermore, such a workshop gave the opportunity to bring together international specialists to facilitate discussions and new collaborations. The information collected should familiarize the ERO with the latest important developments in fluorinated surfactants chemistry.

Agenda

Recent Advances in Fluorinated Surfactants

Amphitheater 2EO2 and H. Fabre
Université d'Avignon et des Pays de Vaucluse
France
January 26 and 27 2001

Thursday January 25 2001

4:00-7:00pm Arrival

Friday January 26 2001 (Amphitheater 2EO2)

Session I and II
Friday morning

8:00-9:00am Registration - Centre Sainte Marthe, Université d'Avignon et des Pays de Vaucluse,

9:00-9:15 Introduction by H. Méloni President of the "Université d'Avignon et des Pays de Vaucluse"

Session I
Chairman **Stephen Lee**

9:15-9:45 Introductory remarks
Stephen Lee
U.S. Army Research Office
Research Triangle Park, North Carolina, (USA)

9:45-10:15 1. "*Multicompartment Micelles Based on Hydrocarbon and Fluorocarbon Polymerisable Surfactants*"
Françoise Candau, J. Selb, K. Stähler, Institut Charles Sadron, (C.R.M. - E.A.H.P.), 6, rue Boussingault, 67083 Strasbourg Cedex, (France)

10:15-10:45 2. *"New micellar monomers and polymers bearing perfluorocarbon chains".* A. Kotzev, **André Laschewsky**, R. Rakotoaly. Université catholique de Louvain, Dept. of Chemistry, Place L.Pasteur 1, B-1348 Louvain-la-Neuve (Belgium)

10:45-11:15 Break

Session II
Chairman Fredric M. Menger

11:15-11:45 3. *" Will Fluorocarbon-Based Oxygen Carriers Help Mitigate Blood Shortages?"*
Jean G. Riess, University of California at San Diego and Alliance Pharmaceutical Corp., San Diego, (USA)

11:45-12:15 4. *"Perfluorinated lipids designed for the 2D crystallization of membrane proteins."*
Charles Mioskowski, Faculte de Pharmacie, 74, route du Rhin BP 24, 67 401 ILLKIRCH- (France).

12:15-12:45 5. *"How to control the molecular architecture of a bilayer of a surfactant including proteins"* **Jean-Jacques Benattar**. Service de Physique de l'Etat Condensé, CEA-Saclay, F-91911 Gif sur Yvette Cedex, (France)

Session III and IV, Friday afternoon

Session III
Chairman André Laschewsky

2:30-3:00pm 6. "Fluorinated and semifluorinated compounds: Synthesis, generalization of the amphiphilic concept and applications"
Armand Lattes, I. Rico-Lattes Laboratoire des IMRCP, UMR 5623, 31062 Toulouse Cedex, (France)

3:00-3:30 7. *"Amphiphilic Telomers containing Vinylidene Fluoride Base Units"*
Bruno Améduri, Laboratory of Macromolecular Chemistry ; Ecole Nationale Supérieure de Chimie de Montpellier ; 8, Rue Ecole Normale ; F-34296 MONTPELLIER Cedex 5 (France)

3:30-4:00 8. *"Fluorinated surfactants in fire fighting foam"*
Martial Pabon, Elf Atochem, C.A.L., 92303, Levallois-Perret cedex, (France)

4:00-4:30 Break

Session IV
Chairman: Armand Lattes

4:30-5:00 9. *"Perfluorinated amphipathic molecules with aminoacids or oligopeptides"* **Claude Selve**. Nancy, Université Henri Poincaré - Nancy I - Laboratoire de Chimie Physique Organique et Colloïdale. UMR CNRS-UHP N°7565; Faculté des Sciences - B P 239 F-54506 - VANDOEUVRE les NANCY Cedex. (France)

5:00-5:30 10. *"Adsorption of fluoro-surfactants at air-water and water-CO_2 interfaces"*. **Julian Eastoe**, School of Chemistry, University of Bristol, Bristol BS8 1TS, (UK).

5:30-6:00pm 11. "*Enzymology in Super-Critical Fluid Microemulsions*" David Steytler, Justin Holmes, Julian Eastoe, Gareth Rees and **Brian Robinson**, School of Chemical Sciences, University of East Anglia, Norwich, (UK).

6:00- 12 "Extra" communication, by **F. M. Menger**

Saturday morning - Amphitheatre H. Fabre (Faculté des Sciences)

Session V
Chairman Françoise Candau

9:00-9:30 13. *"Combinatorial Synthesis of Fluorinated Gemini Surfactants"* **Fredric M. Menger**, Carolline Clavel, and Andre Peresypkin Department of Chemistry, Emory University, Atlanta, GA USA

9:30-10:00 14. *"Fluorinated chains as tools for the design of nano-compartmentalized colloidal systems"*, **Marie Pierre Krafft,** Chimie des Systèmes Associatifs, Institut Charles Sadron (CNRS), 6, rue Boussingault, 67083 Strasbourg cedex (France)

10:00-10:30 15. *"Fluorine chemistry at the University of Nice-Sophia Antipolis : Highly fluorinated compounds for molecular organised systems"* **Frederic Guittard**, Geribaldi Serge, Chimie des Materiaux Organiques et Metalliques (CMOM).

10:30-11:00 Break

11:00-12:00 Group Discussion

Abstracts

1. MULTICOMPARTMENT MICELLES BASED ON HYDROCARBON AND FLUOROCARBON POLYMERISABLE SURFACTANTS

F. Candau, J. Selb, K. Stähler
Institut Charles Sadron, (C.R.M. - E.A.H.P.), 6, rue Boussingault, 67083 Strasbourg Cedex, France

Polymers that form micelle-like structures are of particular interest for biological and pharmaceutical applications. They may be used in drug delivery processes due to their ability to solubilize hydrophobic compounds and to an improved stability when compared to their low molecular weight amphiphilic counter-parts.

One way to synthesize these polysoaps is a free radical polymerization of monomeric surfactants (surfmers) or the copolymerization of these surfactants with hydrophilic monomers in aqueous micellar media. In the latter case, the polymer structure is similar to a string of beads where the beads are the covalently linked hydrophobic microdomains distributed along the hydrophilic backbone string. In the present study we have investigated the possibility of synthesizing polymers formed of hydrophobic microdomains of different nature and connected by hydrophilic linear spacers. Such systems could be of particular interest for the specific solubilization of mutually incompatible hydrophobic compounds in controlled drug release.

The synthesis of multicompartment polymeric micelles (MCPM) was achieved by aqueous radical terpolymerization of a water-soluble monomer (acrylamide) with both hydrocarbon (H) and fluorocarbon (F) surfmers in the micellar state. The selected H- and F-surfmers are $CH_2 = CH\text{-}CON(C_2H_5)\text{-}CH_2\text{-}CH_2\text{-}N(CH_3)_2\text{-}CH_2COOC_{16}H_{33}$/Br/Cl and $CH_2 = CH\text{-}CONH\text{-}CH_2\text{-}CH_2\text{-}N(CH_3)_2\text{-}CH_2COOCH_2CH_2\text{-}C_8F_{17}$/Br , respectively. Their mutual incompatibility in aqueous solution was checked by conductivity and surface tension experiments. Two cmc values are found, in favor of the coexistence of two distinct types of micelles at surfactant concentrations above 1 mmol/L (second cmc) over a broad composition range. The solubilization properties of the pure and mixed surfactant systems were studied for different hydrophobic probes. Significant differences in the solubilization capacity occur due to the nature of the dye, of the surfactant and of the micelle shape and composition. A kinetic study on the incorporation behavior of the H- and F- surfmers in the polyacrylamide backbone during a batch polymerization shows a compositional drift as a function of conversion which is attributed to micellar effects. A semi-continuous process was designed which allows the synthesis of copolymers homogeneous in composition. The presence of well segregated H- and F- microdomains in terpolymers could be inferred from viscosity and fluorescence experiments.

2. New Micellar Monomers and Polymers Bearing Perfluorocarbon Chains

A. Kotzev, A. Laschewsky, R. Rakotoaly

Universit• catholique de Louvain, Dept. of Chemistry,
Place L.Pasteur 1, B-1348 Louvain-la-Neuve (Belgium)
e-mail: laschewsky@cico.ucl.ac.be

Up to now, the synthesis of polymerizable fluorocarbon amphiphiles and of their polymers has been little developed. Despite the use of an analogous carbon skeleton and the formal similarity of $-(CH_2)_n-$ and $-(CF_2)_n-$ hydrophobic chains, differences between hydrocarbon and fluorocarbon amphiphiles are profound, and the latter are therefore expected to present particular properties.

We report here on new hydrophobically modified cationic monomers and polymers which bear fluorocarbon substituents. In order to avoid the chemically somewhat fragile $-CH_2-CF_2-$ group, we have focused on perfluorooctanoic acid as hydrophobic fragment which is connected to the functional groups via a tertiary amide linkage. This group is hydrolytically rather stable, while simultaneously providing a certain hydrophilicity to the molecules. Cyclic amides, however, should be avoided in the hydrophilic part as they increase the Krafft temperature markedly. The monomers synthesized display the characteristics of reactive surfactants and emulsifiers.

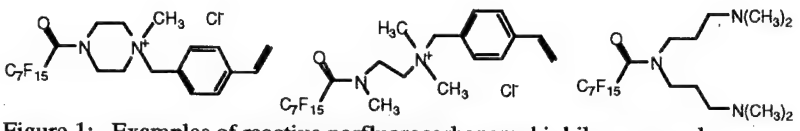

Figure 1: Examples of reactive perfluorocarbonamphiphiles prepared

Amphiphilic fluorocarbon polymers were obtained by three different synthetic strategies: polycondensation (via the Menshutkin reaction), freeradical statistical copolymerization of hydrophilic and hydrophobized cationic monomers, and step-wise quaternization of an uncharged precursor polymer, namely poly(4-chloromethylstyrene). The watersoluble polymers show the characteristics of polymeric amphiphiles, behaving as so-called "polysoaps". For example, the associate mainly intramolecularly due to hydrophobic interactions, giving rise to low viscosity aqueous solutionseven at high polymer contents, though exhibiting a typical polyelectrolyte behaviour. Also, they provide hydrophobic domains enabling the solubilization of water-insoluble compounds. Furthermore, concentrated solutions may display lyotropic mesophases.

In addition to fluorocarbon homopolymers and their hydrocarbon analogs, amphiphilic polymers bearing mixed hydrocarbon and fluorocarbon chains were prepared, as well as segmented block copolymers. This opens the possibility to profit from the mutual incompatibility of the hydrocarbon and fluorocarbon fragments, enabling the design of multicompartment micelles. The latter are novel structures which allow to create aqueous one-phase-but-three-compartment-systems of low viscosity.

Some key properties of the monomeric and polymeric amphiphiles with various molecular architecture will be discussed, e.g.with respect to solubility, to surface activity, and to solubilization capacity.

References:

1) A.Kotzev, A.Laschewsky, *Polym.Prepr.Am.Chem.Soc.Polym.Chem.Div.* (1998) 39(2), 942-943
2) T. Fršmyr, F.K. Hansen, A.Kotzev, A.Laschewsky, *Polym.Mat.Sci.Eng.* (1999) 81, 513-514

3. Will Fluorocarbon-Based Oxygen Carriers Help Mitigate Blood Shortages?

Jean G. Riess, University of California at San Diego and Alliance Pharmaceutical Corp., San Diego

Blood has become safe but rare, and shortages are predicted to increase in frequency. Fluorocarbon emulsions are expected to provide a simple, safe and immediately effective means of delivering oxygen to tissues during surgical operations when used in conjunction with acute normovolemic hemodilution (the "Augmented"-ANH procedure). The principal challenges in the development of such oxygen carriers were to identify a rapidly excreted fluorocarbon that could be manufactured on a large scale with high purity, to produce small-size, stable, ready-for-use, sterile emulsions, and to understand fluorocarbon "physiology". A recently completed Phase III clinical trial conducted in Europe in general surgery patients demonstrated significant avoidance ($p = 0.002$) and reduction ($p < 0.001$) of blood transfusion in the patients with modest to high blood loss (86% of the study population) receiving OxygentTM AF0144, a 60% w/v emulsion of perfluoroalkyl bromides.

Sources for references: Riess, J.G. and Keipert, P.E. (1998) In: E. Tsuchida (Ed.) Blood Substitutes - Present and Future Perspectives. Elsevier, Amsterdam, Chap. 7, pp. 91-101; Krafft, M.P. and Riess, J.G. (1998) Biochimie. 80, 489-514; Riess, J.G. (2000) In: R.E. Banks (Ed.) Fluorine at the Millennium. Elsevier, Amsterdam. Chap. 23

4. Perfluorinated lipids designed for the 2D crystallization of membrane proteins

Charles Mioskowski, Faculte de Pharmacie, 74, route du Rhin BP 24, 67 401 ILLKIRCH-(France).

5. How to control the molecular architecture of a bilayer of a surfactant including proteins

Jean-Jacques Benattar

[1]Service de Physique de l'Etat Condensé, CEA-Saclay,

F-91911 Gif sur Yvette Cedex, France

ABSTRACT

We report a generally applicable protein insertion process leading to the formation of a close packed protein single layer within a freestanding surfactant bilayer (Newton Black Film). Very high packing fractions can be obtained in a controlled manner, simply by adjusting the protein chemical potential in the solution. Using X-ray reflectivity, we observed a time dependent insertion of the proteins within the NBF and then a stable equilibrium state. This process allows the control of well defined and devoted new architectures of biological interest. We first applied this method to the confinement of a model protein in a Newton Black Film (NBF) of a non-anionic surfactant, then to phospholipids and finally we will discuss the case of films made of fluorosurfactants.

6. FLUORINATED AND SEMIFLUORINATED COMPOUNDS : SYNTHESIS, GENERALIZATION OF THE AMPHILILIC CONCEPT AND APPLICATIONS.

Armand LATTES and Isabelle RICO-LATTES

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31062 TOULOUSE cedex 4 (France).

One of the objective of our laboratory being the development of novel mixed fluorinated and hydrogenated molecule we prepared new fluorinated Wittig reagents, very useful for the synthesis, in formamide, of mixed molecules. Then we prepared olefins from which we studied :

* the cycloaddition reaction with cyclopentadiene, and the aggregation properties of obtained substitued norbornenes (primitive surfactants),
* the amidation reaction in formamide microemulsions ;
* their ability to provide new formulations for blood substitutes or their applications in vitreous surgery.

We also prepared new surfactants having polar heads from lactose and glucose derivatives. An interesting phenomenon of gelification in formamide was observed with surfactants synthesized from gluconolactone.

Perfluorinated or semifluorinated hydrocarbons have special properties owing to the characteristics of the fluorine atom : particularly the hydrophobicity of the fluorinated chains and their segregation behaviour towards perhydrogenated compounds. We explored these properties in order to develop new syntheses and new applications in biology or medecine. Our last results in this field was the preparation of a new mixed double chain catanionic derivative. This compound forms spontaneous veiscles useful to encapsulate AZT after sonication. The stability and morphology of these vesicles have been studied by dynamic light scattering and TEM freeze fracture replica

7. AMPHIPHILIC TELOMERS CONTAINING VINYLIDENE FLUORIDE BASE-UNITS

M. DUC, B. AMEDURI, B. BOUTEVIN

Laboratory of Macromolecular Chemistry ; Ecole Nationale Supérieure de Chimie de Montpellier ; 8, Rue Ecole Normale ; F-34296 MONTPELLIER Cedex 5 (France)

After reminding several concepts of the telomerization reaction, that of vinylidene fluoride (or 1,1-difluoroethylene, VDF) with various transfer agents is presented. Firstly, in the presence of methanol, hydroxy end-group PVDF, $HOCH_2(CH_2CF_2)_n$-H were produced. Secondly, from hydrogenodiethyl phosphonate, original $H(VDF)_nP(O)(OEt)_2$ were obtained and then changed into the corresponding fluorinated diacid phosphonates. In both cases, the transfer constants of methanol or $HP(O)(OEt)_2$ were assessed and correlated to the bond dissociation energies of the C-H or P-H bonds of these transfer agents. Hence, well-defined VDF telomers displaying a polar terminal function could be synthesized.

8. FLUORINATED SURFACTANTS IN FIRE FIGHTING FOAMS

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Abstract: Fluorinated surfactants and synthetic fire fighting foams are presented. The fact that fluorine atoms are present in a surfactant molecule modifies its behaviour compared to classical surfactants. It gives to the molecule an outstanding chemical and thermal stability. Fluorine also makes that those surfactants give some very low surface tension in aqueous solution even when used at reduced concentrations.
For those reasons, it is shown that fluorinated surfactants are particularly adapted to the formulation of film forming fire fighting foams in which they are associated to classical hydrocarbon surfactants. The way those surfactant are formulated with hydrocarbon surfactants is explained. Finally, the etancheity of a water film is studied as a function of the surfactant solubilised in this film.

9. Molécules amphipathiques perfluorées sur la base d'aminoacides ou d'oligopeptides

Claude SELVE , Christine GERARDIN , Ludwig RODEHÜSER

* - Université Henri Poincaré - Nancy I - Laboratoire de Chimie Physique Organique et Colloïdale. Fac des Sciences - UMR 7565 CNRS - B P 239 - 54506 - VANDOEUVRE les NANCY Cedex. (France) – Tel:03 83 91 23 60; Fax: 03 83 91 25 32; E mail: Claude.Selve@lesoc.uhp-nancy.fr

Résumé : Une première partie donnera une vue générale de synthèses, généralement par stratégie modulaire, de molécules tensioactives ioniques et non ioniques contenant des aminoacides ou des oligopeptides comportant des chaînes hydrophobes essentiellement perfluorées. Brièvement, quelques propriétés physico-chimiques et biologiques typiques seront présentées. Une deuxième partie traitera plus particulièrement de la préparation de molécules amphipathiques et complexantes des cations métalliques, préparées sur la base d'une tête hydrophile du type peptidoamine.

"Perfluorinated amphipathic molecules with aminoacids or oligopeptides"

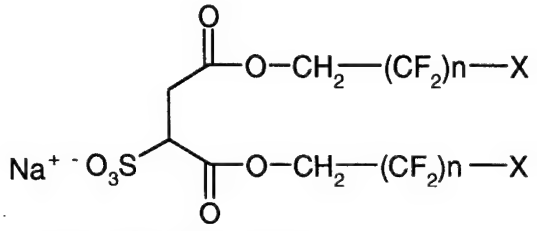
Summary: In a first part, we will present a general view of the syntheses of ionic and non ionic surfactive molecules containing aminoacids or oligopeptides and a perfluorinated chain. These preparations correspond essentially to modular strategies. Some specific physicochemical and biological properties will be presented. In a second part, we will expose more particularly synthesis of perfluorinated amphiphilic and cation-complexing compounds based on peptidoamines as polar head.

10. Adsorption of fluoro-surfactants at air-water and water-CO_2 interfaces

Julian Eastoe*
School of Chemistry, University of Bristol, Bristol BS8 1TS UK.

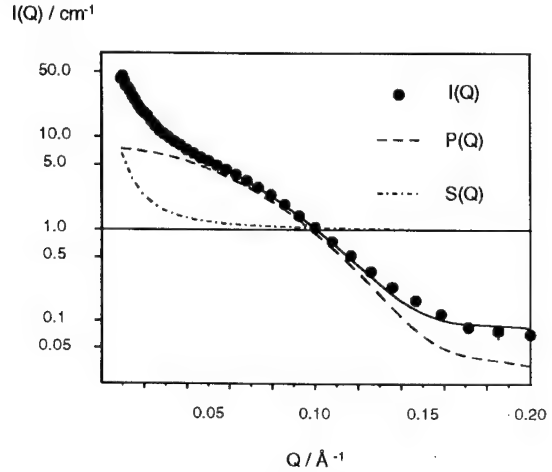
David C. Steytler
School of Chemical Sciences, University of East Anglia, Norwich NR4 7TJ UK.

Microemulsions of water-in-CO_2 are unusual and interesting systems[1]. They have a have a range of potential uses, for example as speciality cleaning fluids[1], or as advanced reaction and separation media[2]. Although hydrocarbon surfactants are ineffective[3], fluorocarbons do stabilise the water-CO_2 interface. For this purpose we have synthesised a range of novel compounds, which are essentially fluorinated analogues of Aerosol-OT[4].



Fluorinated sulfosuccinate : X = F or H

Adsorption and aggregation properties of these surfactants, in both aqueous solutions and water-in-CO_2 microemulsions, have been studied by tensiometry, neutron reflection[5] and high pressure small-angle neutron scattering[4]. It is found that the phase behaviour is very sensitive to the surfactant chemical structure, in terms of chain length and extent of fluorination. The results will be discussed, with the aim of learning how surfactant chemistry can be optimised for water-CO_2 phases.



SANS from water-in-CO_2 microemulsion droplets

[1] T.A.Hoefling, R.M.Enick and E.J.Beckmann, J.Phys,Chem., 1991, 95, 7127, and J.M. deSimone et al. Science, 1996, 274, 2049-2052.
[2] D.C. Steytler et al., Langmuir, 1998, 14, 6371.
3 K.A.Consani and R.D.Smith, J.Supercrit.Fluids, 1990, 3, 51
4 J.Eastoe and D.C.Steytler et al. Langmuir, 1996, 12, 1423.
5 J.Eastoe et al., Langmuir, 1999, 15, 7591.

11. Enzymology in Super-Critical Fluid Microemulsions.

David Steytler, Justin Holmes, Julian Eastoe, Gareth Rees and Brian Robinson

Water-in-oil microemulsions have been prepared in carbon dioxide using an aerosol-OT derived surfactant based on hydrocarbon and fluorocarbon chains. Enzymes have been successfully incorporated in these microenmulsions with retention of activity. Reactions catalysed by alpha-chymotrypsin and lipoxygenase will be reported.

13. Combinatorial Synthesis of Fluorinated Gemini Surfactants

Fredric M. Menger, Caroline Clavel, and Andre Peresypkin

Department of Chemistry, Emory University, Atlanta, GA USA

Abstract.

Combinatorial methods were applied to the development of new catalytic systems. This work led further to the development of a "structural phase diagram" in which over 40 combinatorially synthesized
surfactants were examined for phase behavior (micelles, vesicles, coacervates etc.). The phase diagram shows in detail how phase and molecular structure are interrelated. Among the host of combinatorially developed surfactants are a series of fluorinated zwitterionic geminis whose unique properties will be discussed. These gemini surfactants were synthesized by Caroline Clavel while visiting Emory last summer from Montpellier University. Andre Peresypkin, a graduate student at Emory, is doing the characterizing work.

14. FLUORINATED CHAINS CAN GENERATE NANO-COMPARTMENTALIZED COLLOIDAL SYSTEMS

M.P. KRAFFT, M. SCHMUTZ. Chimie des Systèmes Associatifs. Institut Charles Sadron (CNRS). 6 rue Boussingault, 67083 Strasbourg, France. krafft@ics.u-strasbg.fr

F. GIULIERI. Université de Nice. Parc Valrose, 06034 Nice, France.

M. GOLDMANN, P. FONTAINE. LURE, 91898 Orsay, Paris-Sud, France.

We have taken advantage of the unique structural characteristics of fluorinated chains, and of their extreme *hydro*phobicity and *lipo*phobicity, to generate diverse phase-separated molecular systems, including Langmuir monolayers, vesicles, microtubules and emulsions[1,2]. For example, monolayers with a "lift" effect were obtained by combining dipalmitoyl phosphatidylethanolamine (DPPE) with the fluorocarbon/hydrocarbon diblock $C_8F_{17}C_{16}H_{33}$. Compression isotherms and grazing incidence X-ray diffraction studies indicate that, when pressure is increased, the diblock, initially present on the water surface, is progressively ejected from the DPPE monolayer and forms a second organized layer on top of a DPPE-only monolayer. The phenomenon is reversible. This is, to our knowledge, the first example of reversible vertical micro phase separation observed in a monolayer. Polymerization of a hydrophobic monomer (isodecyl acrylate) within the bilayer of vesicles made from a perfluoroalkylated phosphatidylcholine produced true polymer microcapsules instead of the phase-separated hybrid particles constituted by latex polymer beads attached to the vesicles that have been observed up to now with hydrogenated lipids[3]. The bilayer of fluorinated vesicles with its internal fluorinated core surrounded by two non-expandable lipophilic shells thus provides a new ordered matrix that can orient polymerization and generate, for the first time, hollow polymeric capsules from monomer-loaded vesicles.

[1]M.P. Krafft, J.G. Riess, *Biochimie*, 1998, **80**, 489-514.

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[3] M. Jung, D.H.W. Hubert, P.H.H. Bomans, P.M. Frederik, J. Meuldijk, A.M. van Herk, H. Fischer, A.L. German, *Langmuir*, 1997, **13**, 6877-6880.

15. Fluorine chemistry at the University of Nice-Sophia Antipolis : Highly fluorinated compounds for molecular organised systems

F. Guittard and S. Géribaldi

Summary :For many years, the principal research direction of our Group in the laboratory "Chimie des Matériaux Organiques et Métalliques" at the University of Nice-Sophia Antipolis concerns the synthesis of highly fluorinated functional compounds, and their use for the elaboration of Molecular Organised Systems (MOSs). Whatever the type of MOSs to which the synthesised product is devoted, the structure of this substrate is elaborated always using the Molecular Design Strategy in order to optimise the probability for fit between the prepared structure and its potential application.
The highly fluorinated compounds prepared can be classified according to four types of structures related to the MOSs applications :
-surfactants used for vesicle preparation, oxygen carrier emulsions, biocides and additive agents in varnishes for optical materials,
-thermotropic liquid crystals as monomeric or polymeric forms for device applications,
-sulfur-containing molecules for self-assembled monolayers (SAMs) for the modification of metal surfaces,
-polyfunctionalised monomers for synthesis of fluorinated polymers with variable surface tension and hydrophobicity.
Some recent results are presented to illustrate the different fields of application.

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Highly fluorinated amphiphiles and colloidal systems, and their applications in the biomedical field. A contribution

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Summary — Fluorocarbons and fluorocarbon moieties are uniquely characterized by very strong intramolecular bonds and very weak intermolecular interactions. This results in a combination of exceptional thermal, chemical and biological inertness, low surface tension, high fluidity, excellent spreading characteristics, low solubility in water, and high gas dissolving capacities, which are the basis for innovative applications in the biomedical field. Perfluoroalkyl chains are larger and more rigid than their hydrogenated counterparts. They are considerably more hydrophobic, and are lipophobic as well. A large variety of well-defined, modular fluorinated surfactants whose polar head groups consist of polyols, sugars, sugar phosphates, amino acids, amine oxides, phosphocholine, phosphatidylcholine, etc, has recently been synthesized. Fluorinated surfactants are significantly more surface active than their hydrocarbon counterparts, both in terms of effectiveness and of efficiency. Despite this, they are less hemolytic and less detergent. Fluorosurfactants appear unable to extract membrane proteins. Fluorinated chains confer to surfactants a powerful driving force for collecting and organizing at interfaces. As compared to non-fluorinated analogs, fluorosurfactants have also a much stronger capacity to self-aggregate into discrete molecular assemblies when dispersed in water and other solvents. Even very short, single-chain fluorinated amphiphiles can form highly stable, heat-sterilizable vesicles, without the need for supplementary associative interactions. Sturdy microtubules were obtained from non-chiral, non-hydrogen bonding single-chain fluorosurfactants. Fluorinated amphiphiles can be used to engineer a variety of colloidal systems and manipulate their morphology, structure and properties. Stable fluorinated films, membranes and vesicles can also be prepared from combinations of standard surfactants with fluorocarbon/hydrocarbon diblock molecules. In bilayer membranes made from fluorinated amphiphiles the fluorinated tails segregate to form an internal teflon-like hydrophobic and lipophobic film that increases the stability of the membrane and reduces its permeability. This fluorinated film can also influence the behavior of fluorinated vesicles in a biological milieu. For example, it can affect the *in vivo* recognition and fate of particles, or the enzymatic hydrolysis of phospholipid components. Major applications of fluorocarbons currently in advanced clinical trials include injectable emulsions for delivering oxygen to tissues at risk of hypoxia; a neat fluorocarbon for treatment of acute respiratory failure by liquid ventilation; and gaseous fluorocarbon-stabilized microbubbles for use as contrast agents for ultrasound imaging. Fluorosurfactants also allow the preparation of a range of stable direct and reverse emulsions, microemulsions, multiple emulsions, and gels, some of which may include fluorocarbon and hydrocarbon and aqueous phases simultaneously. Highly fluorinated systems have potential for the delivery of drugs, prodrugs, vaccines, genes, markers, contrast agents and other materials (© Société française de biochimie et biologie moléculaire / Elsevier, Paris).

fluorocarbons / fluorinated amphiphiles / fluorocarbon emulsions / gels / vesicles / liposomes / tubules / bilayers / Langmuir monolayers / oxygen delivery / drug delivery / diagnosis

Introduction

Fluorine is the most electronegative of all elements, and its dense electron cloud has very low polarizability. Replacing the hydrogen atoms by fluorines is certainly one of the most dramatic perturbations which can be inflicted on an organic molecule. Perfluorocarbons (hydrocarbons in which all hydrogens are replaced by fluorines) and perfluorocarbon moieties have very strong intramolecular bonds and very weak intermolecular interactions. It is no wonder that perfluorocarbons (fluorocarbons) have properties that differ significantly from those of the parent hydrocarbons, and in many unique ways. Fluorocarbons substantially surpass hydrocarbons in terms of stability, surface activity and hydrophobicity. They also have higher fluidity, lower dielectric constants, higher compressibility and higher gas-dissolving capacities. Fluorocarbons are not only extremely hydrophobic, they are lipophobic as well. This provides a potent driving force for fluorocarbon moieties to segregate from both lipidic and hydrophilic moieties, and for fluorinated amphiphiles to self-assemble into highly stable and well organized films, bilayers, and discrete supramolecular systems such as vesicles, tubules, etc. Fluorinated amphiphiles provide versatile tools for adjusting the properties of such organized disperse systems. Fluorocarbons and fluorinated surfactants (fluorosurfactants) also allow the formulation of a wealth of multi-component, multi-phase compartmentalized colloidal systems.

This short, non-exhaustive review intends to illustrate the role that highly fluorinated components may play in colloid and surface chemistry. It consists primarily of an account of the authors' own efforts and experience in the

field, hence will be limited to some specific aspects of this chemistry. It also intends to outline the potential applications of highly fluorinated compounds and systems in biomedical research and in the development of novel therapies.

Fluorocarbons and fluorosurfactants

Specific characteristics of fluorocarbons

Carbon-fluorine bonds are, on average, more stable than carbon-hydrogen bonds by approximately 75 kJ mol^{-1} [1]. Perfluorination also reinforces the skeleton's C-C bonds as a consequence of strong inductive effects. The stronger intramolecular bonds in fluorocarbons, as compared to hydrocarbons, are largely responsible for the exceptional thermal and chemical stability of fluorocarbons. Fluorocarbons resist to extremely corrosive environments. No bacteria are known to feed on fluorocarbons, and no enzymatic degradation of such compounds has been reported.

Fluorine's electronegativity, its larger size as compared to hydrogen, and its dense electron cloud result in a compact, repellent sheath of electrons that protects the perfluorinated moiety and its surroundings against the approach of other molecular species, including reagents. This sort of 'Scotchguard®' effect, at the molecular level, certainly contributes to rendering perfluoroalkyl chains inert.

Perfluoroalkyl (*F*-alkyl) chains, *ie* chains in which all the hydrogen atoms have been replaced by fluorine atoms, are bulkier and more rigid than their hydrogenated counterparts, with cross-sections of *ca* 30 $Å^2$ *vs* 20 $Å^2$. The *F*-alkyl chain's conformational freedom is strongly reduced, as well as the occurrence of gauche defects [2].

The low polarizability of the fluorine atom results in low van der Waals forces between molecules and low cohesive energy densities in liquid fluorocarbons [3]. This is responsible for many of the most valuable and unmatched properties of fluorocarbons, including their low surface tension, high fluidity and spreading characteristics, extreme hydrophobicity and simultaneous lipophobicity, high vapor pressure, high compressibility and exceptional gas-dissolving capacities. Additional properties relevant to fluorocarbons' potential in the biomedical field include high density, nonadherence and antifriction properties, and magnetic susceptibility values close to those of water.

The perfluorochemicals that are being evaluated for *in vivo* oxygen delivery, liquid ventilation, diagnosis and drug delivery can be linear or cyclic, and may contain some hydrogen, halogen, oxygen, or nitrogen atoms. The compounds which have been most thoroughly investigated for biomedical applications are shown in figure 1 [4].

Fluorosurfactants

Introducing a *F*-alkyl chain into a molecule usually renders this molecule strongly amphiphilic or further enhances an existing amphiphilic character [5, 6]. Fluorosurfactants (surfactants with one or more *F*-alkyl hydrophobic chains) are considerably more surface active than their hydrogenated analogs. Surface tensions in the 15 to 20 mN m^{-1} range can easily be attained.

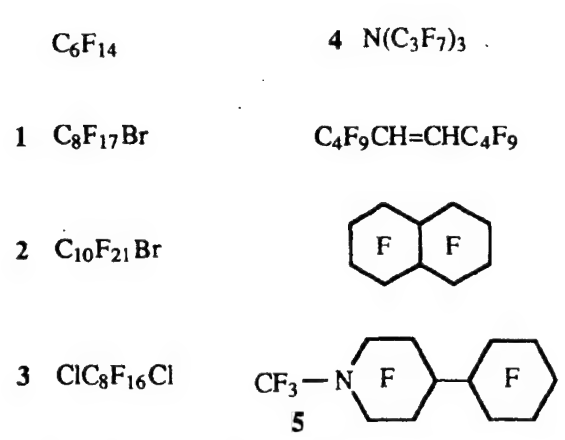


Fig 1. Fluorocarbons most thoroughly investigated for use in therapeutic applications [4, 44].

Fluorosurfactants are of course best suited for effectively reducing fluorocarbon/water interfacial tensions, as for preparing fluorocarbon emulsions and microemulsions; interfacial tension values on the order of 1 mN m^{-1} are readily obtained. Fluorosurfactants are also very efficient, as their critical micellar concentration (cmc) is commonly two orders of magnitude lower than for hydrocarbon surfactants of similar length. Fluorosurfactants present enhanced resistance to biological fluids or corrosive environments.

The mixing of fluorocarbons and hydrocarbons is highly non-ideal [7], resulting largely from the difference in cohesive energy between the two types of molecules. Likewise, fluorinated amphiphiles and hydrogenated amphiphiles show only limited miscibility. When present simultaneously in micelles [8], monolayers, or liposomes, the two types of amphiphiles tend to form phase-separated domains [9]. Such phase separated liposomes were used to simulate the hole formation process that occurs when a macrophage attacks a tumor cell [9].

In self-assemblies of amphiphiles which have both fluorocarbon and hydrocarbon segments in their structure, fluorinated chains tend to regroup and segregate from both the hydrophilic and the lipidic moieties, each clustering in a separate zone. The case of bilayer membranes is illustrated in figure 2. This segregation phenomenon is also expected to reduce the jutting that normally exists between fatty acid chains in bilayers made from phospholipids.

As noted, fluorocarbons and fluorocarbon moieties are significantly more hydrophobic than their hydrogenated analogs. The solubility of CF_4 in water, for example, is one

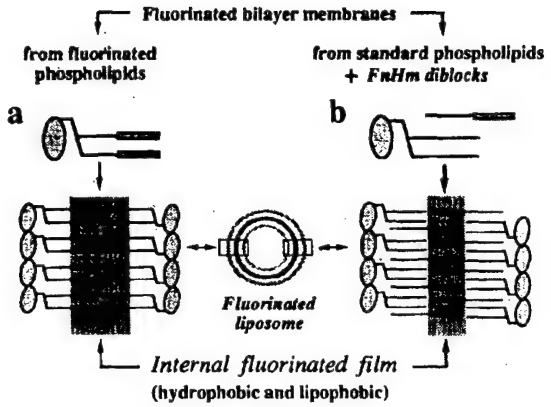


Fig 2. Fluorinated bilayer membranes and fluorinated liposomes can be obtained from fluorinated phospholipids (**a**) and from a combination of standard phospholipids and fluorocarbon-hydrocarbon diblocks (**b**). In both cases, the clustering of the fluorinated chains (grey bars) results in the formation of a hydrophobic and lipophobic internal fluorinated, teflon-like film within the bilayer membrane. From [26].

order of magnitude lower than that of CH_4 [10]. The hydrophobic effect of an alkyl chain (a complex notion whose components are still poorly understood) is generally considered to be roughly proportional to its area in contact with water [11, 12].

It should be emphasized that fluorocarbons and *F*-alkyl chains are not only strongly hydrophobic but lipophobic as well. Therefore, they can develop a lipophobic effect on top of their hydrophobic effect. The former is clearly illustrated, for example, by the fact that certain simple mixed fluorocarbon-hydrocarbon diblock compounds of the $C_nF_{2n+1}C_mH_{2m+1}$ type (FnHm, fig 3), form micelles [13] and fibrous gels [14] when dispersed in a fluorocarbon or a hydrocarbon.

Synthesis of fluorosurfactants

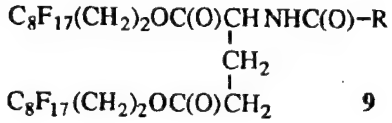
Numerous pure fluorosurfactant molecules have recently been reported in the literature (see for examples and for further references [5, 6, 15–24]). Most commercial products consist, on the other hand, of complex, often poorly defined mixtures, not well suited for physicochemical determinations or biomedical experimentation.

$C_nF_{2n+1}C_mH_{2m+1}$ n = 6, 8, 10; m = 2, 4, 10 — **6 (FnHm)**

$C_nF_{2n+1}CH=CHC_mH_{2m+1}$ n = 6, 8, 10; m = 2, 4, 10 — **7 (FnHmE)**

$C_nF_{2n+1}CH_2CH=CHC_mH_{2m+1}$ — **8**

$C_6F_{13}CH=ClC_6H_{13}$



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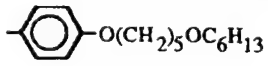
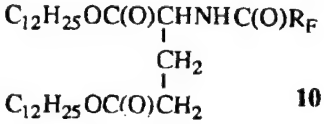
a: $R = -C_2H_7CH=CHC_8H_{17}$

b: 



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a: $R_F = -C_8F_{17}$

b: $R_F = -CF(OCF_2CF)_2OC_3F_7$ (CF_3, CF_3)

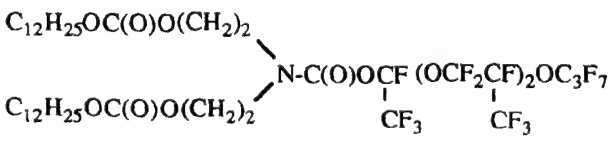


Fig 3. Mixed fluorocarbon-hydrocarbon diblock molecules utilized as components of disperse systems [35, 40–42].

As part of a program aimed at developing novel or improved fluorocarbon systems susceptible of biomedical applications, the synthesis of a variety of well-defined pure fluorosurfactants was undertaken, including neutral, anionic, cationic and zwiterionic compounds, single or double-tailed, with tails identical or not, and with a diversity of polar head groups [6, 16, 24]. A modular molecular design (fig 4) [16, 25] was elected, that allows stepwise variation in hydrophilic, lipophilic and fluorophilic characters, size and shape, chemical functions available for further derivatization, etc. The polar heads included diverse types of polyols, sugars, amino acids, amine oxides, phosphatides, polyhydroxylated telomers, etc [6, 24]. Figure 5 shows typical examples of such materials. Any desirable bioactive agent, immunological or other marker may of course be grafted onto fluorosurfactants just as they can be grafted onto standard amphiphiles.

Fluorosurfactants constitute versatile new components for the preparation of vesicles, fibers, tubules, ribbons, helices and other supramolecular aggregates. These compounds can be used to manipulate the characteristics of such systems and to modify those of standard hydrocarbon systems. Fluorosurfactants are also unique for the formulation of multi-phase, multi-component colloidal systems, including direct and reverse fluorocarbon emulsions, multiple emulsions, microemulsions, gels, aerosols, etc (fig 6), many of which express potential for drug delivery and targeting [25–31]. A parallel research objective is, from a more fundamental standpoint, to determine and understand the impact of the fluorinated moieties on the formation and behavior of the colloidal systems of which they are a part.

A definite prerequisite for fluorosurfactants to be used in biomedical research and in pharmaceuticals is that they be pure and well characterized. This supposes synthetic strategies and laboratory practices that integrate these requirements from the outset. Convenient starting materials to produce fluorosurfactants are available primarily in the form of perfluoroalkyl iodides, $C_nF_{2n+1}I$ (R_FI), and acids $C_nF_{2n+1}COOH$. Compounds of the $C_nF_{2n+1}C_2H_4X$ type, with X = I, OH, SH, COOH, etc, are also commercially available and constitute valuable reagents as the C_2H_4 spacer shields the X group from the influence of the *F*-alkyl chain. The reactivity of X is then usually back to normal, and standard synthetic procedures can be applied. Hydrophobes with longer alkyl spacers are easily obtained by adding R_FI onto appropriate terminally unsaturated alkyl chains. The synthesis and purification of fluorosurfactants can, however, be frustratingly complicated due to high surface activity and decreasing solubility that is usually observed when the length of the *F*-alkyl chain increases.

Fluorocarbon-hydrocarbon diblocks

The simple (perfluoroalkyl)alkanes **6–8** (fig 3) are amphiphiles, not in the usual sense, associating hydrophilic and lipophilic moieties, but in an extended sense in which one

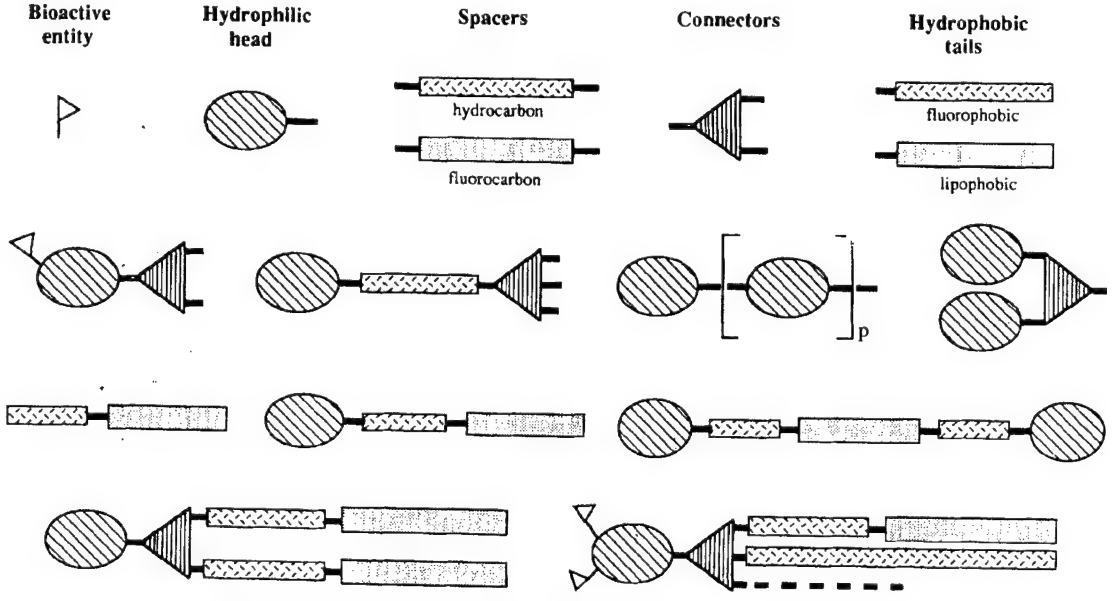
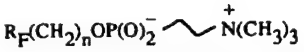


Fig 4. A modular construction set for fluorinated amphiphiles that allows stepwise adjustment of properties. From [25].

Phosphocholine

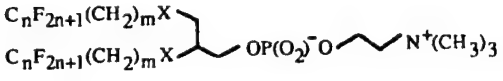


11 (FnCmPC)

n = 1 ; $R_F = C_9F_{19}$
n = 2 ; $R_F = C_4F_9, C_6F_{13}, C_8F_{17}, C_{10}F_{21}$
n = 5 ; $R_F = C_8F_{17}, C_{10}F_{21}$
n = 11; $R_F = C_4F_9, C_6F_{13}, C_8F_{17}, C_{10}F_{21}$

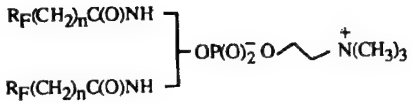
n = 2 ; p = 2, 7 ; $R_F = C_8F_{17}$
n = 5 ; p = 7, 16 ; $R_F = C_8F_{17}$

Phosphatidylcholine



X = COO, CO **12**

n = 4 ; $R_F = C_4F_9, C_6F_{13}, C_8F_{17}$
n = 5 ; $R_F = C_6F_{13}$
n = 10 ; $R_F = C_4F_9, C_6F_{13}, C_8F_{17}$

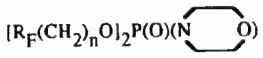


n = 10 ; $R_F = C_4F_9, C_6F_{13}$

Morpholinophosphates

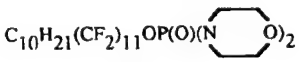
13 (FnCmDMP)

n = 1 ; $R_F = C_7F_{15}, C_9F_{19}$
n = 2 ; $R_F = C_4F_9, C_6F_{13}, C_8F_{17}, C_{10}F_{21}$
n = 5 ; $R_F = C_8F_{17}$
n = 11 ; $R_F = C_6F_{13}, C_8F_{17}$



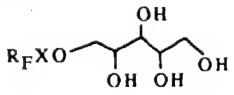
14 (FnCmMMP)

n = 1 ; $R_F = C_9F_{19}$
n = 2 ; $R_F = C_6F_{13}, C_8F_{17}$



15

Xylitol



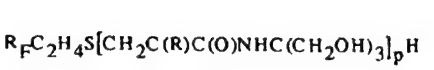
16

X = $(CH_2)_nCO$
$R_F = C_4F_9, C_6F_{13}, C_8F_{17}$

X = CH=CH CH_2
n = 2 ; $R_F = C_5F_{11}, C_8F_{17}$
n = 10 ; $R_F = C_4F_9, C_6F_{13}$

Fig 5. Typical examples of recently synthesized fluorosurfactants intended for use in biomedical research and in pharmaceuticals [6, 24].

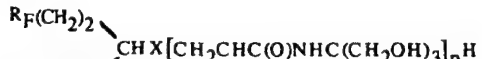
Telomers derived from tris(hydroxymethyl)aminomethane



17

$R_F = C_6F_{13}, C_8F_{17}, C_{10}F_{21}$

$R = H, CH_3$ $\quad p = 4\text{-}12$



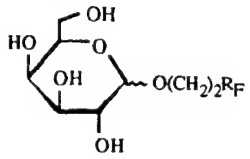
18

$X = S$; $R_F = C_8F_{17}$; $n = 10$; $p = 20$

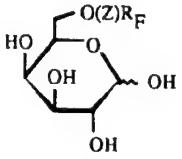
$X = NHC(O)(CH_2)_2S$; $R_F = C_6F_{13}, C_8F_{17}$

$n = 8, 10$; $p = 10\text{-}11$

Galactose



$R_F = C_6F_{13}, C_8F_{17}$

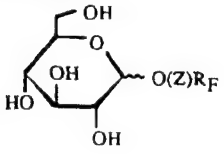


$Z = (CH_2)_2CH{=}CH$; $R_F = C_4F_9, C_6F_{13}, C_8F_{17}$

$Z = C(O)(CH_2)_n$; $n = 2$; $R_F = C_8F_{17}$

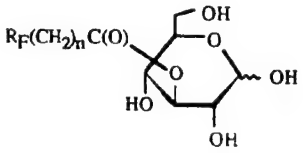
$Z = C(O)(CH_2)_n$; $n = 10$; $R_F = C_4F_9, C_6F_{13}$

Glucose



$Z = (CH_2)_2$; $R_F = C_6F_{13}, C_8F_{17}$

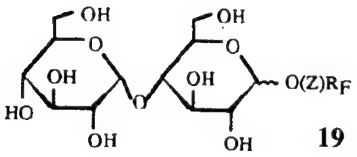
$Z = (CH_2)_2CH{=}CH$; $R_F = C_6F_{13}, C_8F_{17}$



$n = 2$; $R_F = C_8F_{17}$

$n = 10$; $R_F = C_4F_9, C_6F_{13}$

Maltose



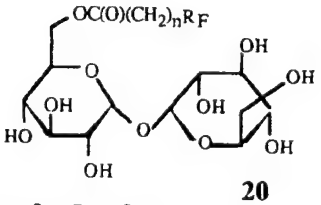
19

$Z = (CH_2)_2$; $R_F = C_6F_{13}, C_8F_{17}$ (α, β)

$Z = (CH_2)_nCH{=}CH$; $n = 3$; $R_F = C_6F_{13}$ (β)

$Z = (CH_2)_nCH{=}CH$; $n = 9$; $R_F = C_6F_{13}, C_8F_{17}$ (β)

Trehalose



20

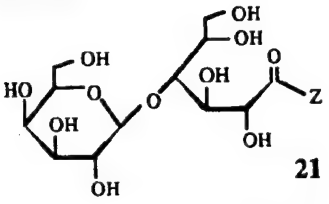
$n = 2$; $R_F = C_8F_{17}$

$n = 4$; $R_F = C_6F_{13}, C_8F_{17}$

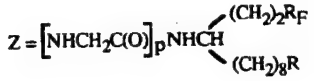
$n = 10$; $R_F = C_4F_9, C_6F_{13}$

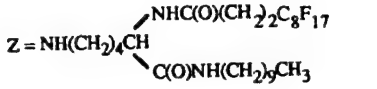
Fig 5. Continued.

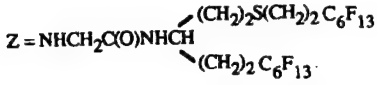
Lactose



21

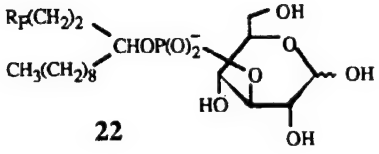






p = 1 ; R = CH_3 ; $R_F = C_6F_{13}, C_8F_{17}$
p = 1 ; R = $CH=CH_2$; $R_F = C_6F_{13}, C_8F_{17}$
p = 2 ; R = CH_3 ; $R_F = C_6F_{13}$

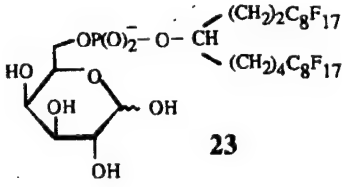
Glucophospholipids



22

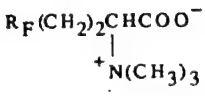
$R_F = C_6F_{13}, C_8F_{17}$

Galactophospholipids



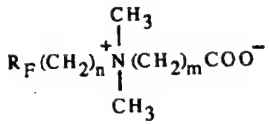
23

Alanine



$R_F = C_4F_9, C_6F_{13}, C_8F_{17}$

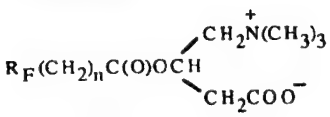
Betaine



24

n = 2 ; m = 1 ; $R_F = C_4F_9, C_6F_{13}, C_8F_{17}$
n = 3 ; m = 3 ; $R_F = C_8F_{17}$
n = 3 ; m = 4 ; $R_F = C_8F_{17}$
n = 3 ; m = 5 ; $R_F = C_8F_{17}$

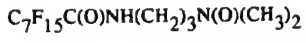
Carnitine



25

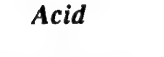
n = 4 ; $R_F = C_6F_{13}, C_8F_{17}$
n = 10 ; $R_F = C_6F_{13}, C_8F_{17}$

Amine oxide



26

Acid



27

Ammonium

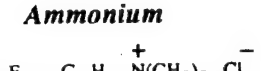


Fig 5. Continued.

of the contraries is lipophilic and the other fluorophilic. The surface activity of mixed fluorocarbon-hydrocarbon diblocks is illustrated by their capacity to reduce the surface tension of hydrocarbons [32]. These diblock compounds present a strong dipole moment. They have also a dielectric constant higher than those of both the totally fluorinated and the totally hydrogenated analogs [1]. The amphiphilic character of the compounds of figure 3 is further illustrated by their capacity to self-assemble in both hydrocarbon and fluorocarbon media. $C_8F_{17}C_{16}H_{33}$, for example, forms micelles in toluene, and reverse micelles in perfluorooctane [13], as well as bilayer-type crystal structures [33, 34]. Bilayer-based fibers were reported to form in benzene and 2-butanone from amphiphiles **9** and **10** (fig 3), which bear two (or one) fluorocarbon chains and one (or two) hydrogenated chain grafted onto a chiral L-glutamate residue [35].

$C_nF_{2n+1}C_mH_{2m+1}$ (FnHm, **6**, fig 3) diblocks can fulfill multiple functions: they were shown to strongly stabilize fluorocarbon emulsions and to allow precise control of the emulsion's particle size [36]; they also allow the preparation of lipid-in-fluorocarbon emulsions [37]; when added to the fluorocarbon phase of such emulsions they enhance the solubility of lipophilic drugs; when incorporated into liposomal membranes, they strongly increase the shelf stability of the liposomes, reduce their permeability [38], and can modify their behavior in a biological milieu [39]. The synthesis and purification of mixed fluorocarbon-hydrocarbon diblocks is straightforward [40–42].

Biocompatibility and pharmacology of fluorosurfactants

The biocompatibility of liquid fluorocarbons is well documented as a result of the intensive efforts that have been devoted to the development of injectable, 'drinkable', or 'breathable' oxygen carriers and imaging agents [26, 27, 43–51]. In contrast, research regarding the pharmacokinetics and toxicity of fluorosurfactants is still very limited.

The available data indicate that introduction of a fluorinated chain into a surfactant does generally not increase its acute toxicity, rather the opposite, despite considerably increased surface activity [6]. Intravenous LD_{50} values in mice depend strongly on the polar head and the structure of the hydrophobic tail(s) (table I). Values as large as 7.7 g/kg, 4 g/kg and 2 g/kg were reached for compounds of the series **12**, **17** and **13**, respectively. Comparison with hydrocarbon analogs shows a roughly parallel variation of LD_{50} or MTD values. These values are usually higher for the fluorosurfactant than for its hydrocarbon analog on a weight by weight basis; this advantage is less pronounced on a mol per mol

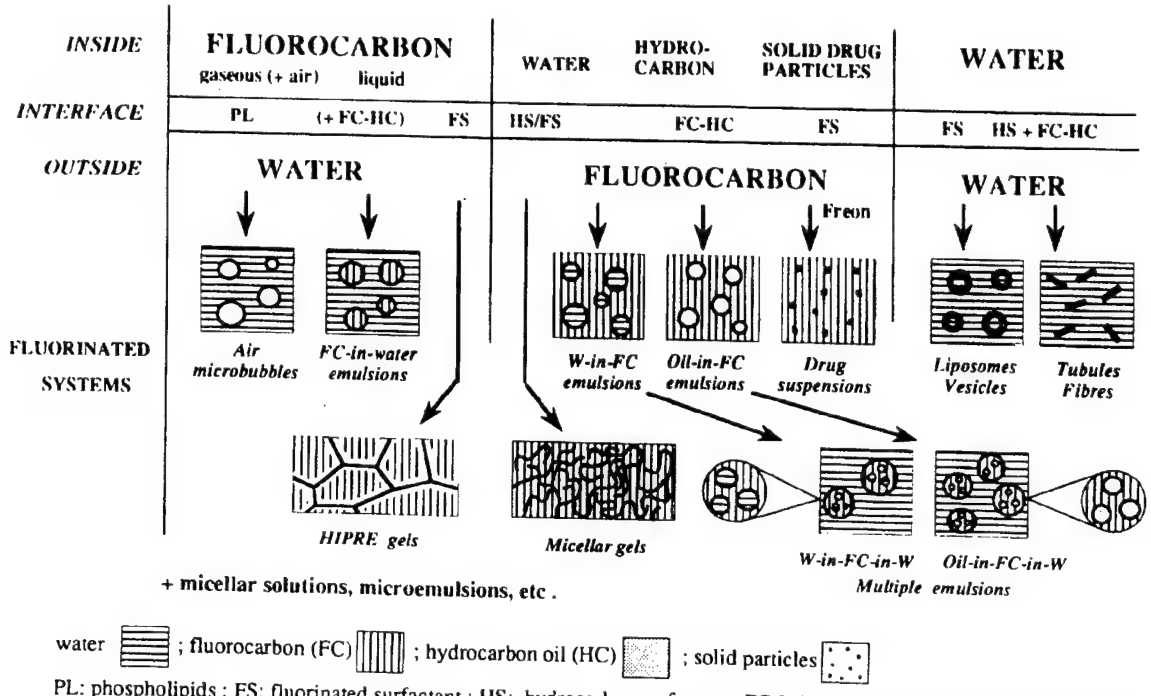


Fig 6. Recently developed colloidal systems based on highly fluorinated materials.

Table I. Acute toxicity of some fluorosurfactants. Examples of LD_{50} (lethal dose for half of the population treated) or MTD (maximum tolerated dose) values measured for typical fluorosurfactants and some hydrocarbon analogs (in italics) [6][a].

Compound	*In vivo toxicity*	
	LD_{50}	*MTD*
$C_4F_9C_{11}H_{22}$-phosphocholine **11**		125 (8/10)
$C_8F_{17}C_2H_4$-phosphocholine **11**	< 50	25
$C_8F_{17}C_5H_{10}$-phosphocholine **11**		125
$C_8F_{17}C_{11}H_{22}$-phosphocholine **11**		25
$(C_6F_{13}C_4H_8)_2$-glycerophosphocholine **12**		> 2800
$(C_8F_{17}C_4H_8)_2$-glycerophosphocholine **12**		> 2800
$(C_4F_9C_{10}H_{20})_2$-glycerophosphocholine **12**	> 7700 (6/10)	
Egg yolk phospholipids	*7000–10000*	
$C_8F_{17}C_2H_4OP(O)[N(C_2H_4)_2O]_2$ **13**		*> 2000 (10/10)
$C_8F_{17}C_{11}H_{22}OP(O)[N(C_2H_4)_2O]_2$ **13**	*4000	> 2000 (10/10)
$(C_6F_{13}C_2H_4O)_2P(O)N(C_2H_4)_2O$ **14**		*> 4000 (8/10)
$(C_9F_{19}CH_2O)_2P(O)N(C_2H_4)_2O$ **14**		*> 2000 (9/10)
$C_8F_{17}CH = CHCH_2$-xylitol-5 **16**	1190	460
$C_8F_{17}C_2H_4S[C_2H_4C(O)NHC(CH_2OH)_3]_6$ **17**	< 2350 (0/10)	> 1820 (10/10)
$C_{10}H_{21}$-$S[C_2H_4C(O)NHC(CH_2OH)_3]_6$	*> 625 (7/10)*	
$C_6F_{13}C_2H_4S[C_2H_4C(O)NHC(CH_2OH)_3]_5$ **17**		3950 (9/10)
$C_8H_{17}S[C_2H_4C(O)NHC(CH_2OH)_3]_4$		*< 1250 (8/10)*
$(C_8F_{17}C_2H_4)(C_9H_{19})CHNHC(O)C_2H_4S[C_2H_4C(O)NHC(CH_2OH)_3]_{14}$	**18**	> 3750
$(C_6F_{13}C_2H_4)(C_9H_{19})CHNHC(O)C_2H_4S[C_2H_4C(O)NHC(CH_2OH)_3]_{10}$	**18**	2500 (9/10)
$C_8F_{17}C_2H_4$-maltose-1 **19**		250
$C_{10}H_{21}$-maltose-1		*< 125 (8/10)*
$C_8F_{17}C_4H_8C(O)$-trehalose-6 **20**		250
$C_8F_{17}C_2H_4SC_2H_4C(O)NHC(CH_2O\text{-galactose})_3$	> 1300 (8/10)	> 500
$C_{12}H_{25}$-$SC_2H_4C(O)NHC(CH_2O$-galactose)$_3$	*< 500 (0/10)*	*> 250*
$C_6F_{13}C_2H_4OP(O)_2^-$-glucose-6	750	
$(C_8F_{17}C_2H_4)(C_8F_{17}C_4H_8)CHOPO_3^-$-galactose-6 **23**		500
$(C_8F_{17}C_2H_4)(C_9H_{19})CHOPO_3^-$-galactose-6	< 250 (2/10)	120
$(C_6F_{13}C_2H_4)(C_9H_{19})CHOPO_3^-$-mannose-6	< 250 (4/10)	120
$C_4F_9\ (CH_2)_2N^+\ (Me)_2CH_2C\ (O)O^-$ **24**	375	250
$C_8F_{17}\ (CH_2)_3N^+\ (Me)_2\ (CH_2)_3C\ (O)O^-$ **24**	250	125
$C_8F_{17}\ (CH_2)_4C(O)$-carnitine **25**		250
$C_{12}H_{25}C(O)$-carnitine	< 125	

[a]iv (tail vein) or *ip in mice (n = 10).

basis. One should, however, keep in mind that, because of their high efficiency, fluorosurfactants can often be used in concentrations 10 to 100 times smaller than those used for classical surfactants.

Perfluoroalkanoic acids, **27**, have received particular attention due to their industrial applications as catalysts in certain polymerization reactions. These acids were found to be rather toxic, with ip LD_{50} values of 190 and 40 mg/kg body weight in rat for perfluorooctanoic (PFOA) and perfluorodecanoic (PFDA) acids, respectively [52]. The patterns of toxicities observed appear to be significantly different for these two acids, and are also species- and sex-dependent. Both acids induced peroxisome proliferation in hepatocytes and considerable changes in enzyme activities. No metabolites were identified. On the other hand, no ill effects were reported in plant workers exposed to PFOA in spite of the considerably higher than normal organic fluorine levels found in their blood [53]. The distribution, metabolism and excretion of PFOA and PFDA have been investigated rather extensively [54, 55].

Other, more limited biodistribution and disposition studies involve the nonionic telomer **17** ($R_F = C_6F_{13}$, P = 5–6) [56]. Rats were given a 100 mg/kg dose of CO (amide)-[^{14}C]-labeled telomer by the iv or ip routes. The compound was found in all organs except the brain. The radioactivity was mainly excreted with the urine. Some $^{14}CO_2$ was found in the expired air. Urine and plasma analysis with an anionic resin showed that part of the telomer had converted into a

polyanionic form, indicating that metabolism had occurred, possibly by hydrolysis of the amide bond. There was no evidence, however, that the *F*-alkyl chain was metabolized.

Hemolytic activity is strongly reduced and often suppressed when fluorinated chains are introduced in a surfactant [28, 57]. For example, no detectable hemolysis was seen with a 30 gL^{-1} micellar solution of **13** (F8C2DMP), while its hydrogenated analog is highly hemolytic at 1 gL^{-1}. Hemolysis by fluorosurfactants is actually seen to decrease as fluorinated chain length, and consequently surface activity, increase within a series. The longer the fluorocarbon chain, the less hemolytic the compound (table II). This is the exact opposite of what usually happens with hydrocarbon surfactants.

Some attention was given to fluorocarbon-hydrocarbon diblock amphiphiles. No effect on the growth and viability was found when such compounds were incubated with Namalva cells [36]. No inhibition of carcinoma cell proliferation was noted with $C_6F_{13}C_{10}H_{21}$, while proliferation decreased by 80% in the presence of decane [58]. The growth and survival of mice was not affected by the intraperitoneal administration of about 30 g/kg body weight doses of $C_6F_{13}CH{=}CHC_{10}H_{21}$(F6H10E) or of F6H10 [36, 59]. Even the iodinated mixed compound $C_6F_{13}CH{=}ClC_6H_{13}$ was tolerated intraperitoneally by mice at a 45 g/kg body weight dose [60].

Table II. Hemolytic activity of fluorinated surfactants as compared to hydrocarbon analogs [6, 28, 57].

Compound	*Hemolytic activity*		
	g L^{-1}	*mmol L^{-1}*	*Grading*[a]
$C_8F_{17}C_2H_4$-phosphocholine **11**	30	47.7	0
$C_8F_{17}C_5H_{10}$-phosphocholine **11**	50	74.5	0
$C_8F_{17}C_{11}H_{22}$-phosphocholine **11**	1	1.32	+++
$C_{10}H_{21}$-phosphocholine	*1*	*1.55*	++++
$C_{16}H_{33}$-phosphocholine	*0.0025*	*0.006*	+++
$(C_6F_{13}C_4H_8)_2$-glycerophosphocholine **12**	60	62.4	0
$(C_8F_{17}C_4H_8)_2$-glycerophosphocholine **12**	60	56.6	0
$(C_4F_9C_{10}H_{20})_2$-glycerophosphocholine **12**	100	105	0
$(C_9H_{19})_2$-glycerophosphocholine	*0.75*	*1.33*	++++
$C_8F_{17}C_2H_4OP(O)[N(C_2H_4)_2O]_2$ **13**	30	44	0
$C_{10}H_{21}OP(O)[N(C_2H_4)_2O]_2$	*1*	*1.33*	++++
$C_8F_{17}C_2H_4S[C_2H_4C(O)NHC(CH_2OH)_3]_6$ **17**	200		0
$C_{10}F_{21}C_2H_4S[C_2H_4C(O)NHC(CH_2OH)_3]_6$ **17**	200		0
$C_{10}H_{21}$-S[$C_2H_4C(O)NHC(CH_2OH)_3]_6$	*1*		++++
$C_6F_{13}C_2H_4$-maltose-1 **19**	100		0
$C_8F_{17}C_2H_4$-maltose-1 **19**	40[b]		0
$C_{10}H_{21}$-maltose-1	*1*		++
$C_6F_{13}C_4H_8C(O)$-trehalose-6 **20**	50		0
$C_8F_{17}C_4H_8C(O)$-trehalose-6 **20**	30[b]		0
$C_4F_9C_{10}H_{20}C(O)$-trehalose-6 **20**	0.1		++++
$C_{10}H_{21}C(O)$-trehalose-6	*1*		++++
$C_6F_{13}C_2H_4OP(O)_2^-$-glucose-6	100		0
$C_8F_{17}C_2H_4OP(O)_2^-$-glucose-6	30[b]		0
$C_{10}H_{21}OP(O)_2^-$-glucose-6	*5*		++++
$C_8F_{17}(CH_2)_3N^+(Me)_2(CH_2)_3C(O)O^-$ **24**	200	358	0
$C_{12}H_{25}N^+(Me)_2(CH_2)_3C(O)O^-$	*1*	*3.25*	+++
$C_8F_{17}(CH_2)_4C(O)$-carnitine **25**	25		0
$C_6F_{13}(CH_2)_{10}C(O)$-carnitine **25**	0.1		++++
$C_{10}H_{21}C(O)$-carnitine	*2*		++++

[a]Grading: 0, +, ++, +++, ++++ correspond to percentages of hemolysis between 0 and 5%, 5 and 15, 15 and 40, 40 and 60, and > 60%, respectively; 0.9% NaCl and distilled water produce 0 and 55% hemolysis, respectively. [b]After dispersion in a Pluronic F-68 solution.

The biodistribution and excretion of the diblock compound F6H10E, was investigated in rats using a 25% w/v emulsion of pure diblock [36, 59]. The animals received a 3.6 g/kg dose of the compound intravenously; tissue distribution was assessed by ^{19}F NMR. A half-life of 25 ± 5 days in the liver, the organ which had taken up most (70%) of the injected dose, was estimated for F6H10E. No new signals were detected in the ^{19}F spectra, indicating that metabolism was absent or minimal, which, if confirmed by more sensitive techniques, should greatly simplify further toxicology and pharmacology studies. The shorter diblock F8H8 was determined to have an organ half-life of about 14 days (Weers JG, personal communication).

Impact of fluorosurfactants on the behavior of particles in a biological milieu

The ability of fluorosurfactants to influence the *in vitro* adsorption of proteins and phagocytic uptake of particles was investigated using calibrated polystyrene microspheres. The microspheres were coated with the surfactant and incubated in swine serum or submitted to phagocytosis by mouse peritoneal macrophages. Both the fluorinated chain and the hydrocarbon spacer length had an effect. Reduced protein adsorption and phagocytic uptake in serum was observed when the microspheres were, for example, coated with $C_8F_{17}C_mH_{2m}PC$, **11** (m = 2 and 5), uptake was then comparable to that observed with a pegylated phospholipid. No effect was seen with a longer spacer, as in **11** (n = 8, m = 11), or with non-fluorinated analogs [61]. Lower phagocytic uptake was also observed when the microspheres were coated with certain of the tris(hydroxymethyl)aminomethane-derived telomers **17** [62].

Drastic reduction of the rate of enzymatic hydrolysis of phospholipids by pancreatic phospholipase A_2 was observed when diblocks of type **6** were introduced in the membrane of a liposome [39]. In order for the phenomenon to be observed, the length of the hydrocarbon moiety of the diblock must be sharply adjusted to that of the phospholipid's fatty acid chains (fig 7). It must have at least ten carbon atoms in the case of DMPC and twelve in the case of DPPC, indicating that this moiety is probably inserted among the fatty acid chains of these compounds. The length of the fluorinated moiety does not appear to be determining but the presence of the fluorinated chain is indispensable, which again illustrates its role as a membrane-structuring element.

The intravascular persistence in mice of carboxyfluorescein-loaded vesicles made of fluorinated phospholipid of type **12** was several times larger than those of similarly sized conventional DSPC or DSPC/cholesterol liposomes [63]. As in the case of 'pegylated' liposomes, the circulation time was independent of the dose administered.

It is certainly remarkable that the internal structure of a fluorinated film can have such impact on the behavior of particles *in vivo* or in a biological milieu.

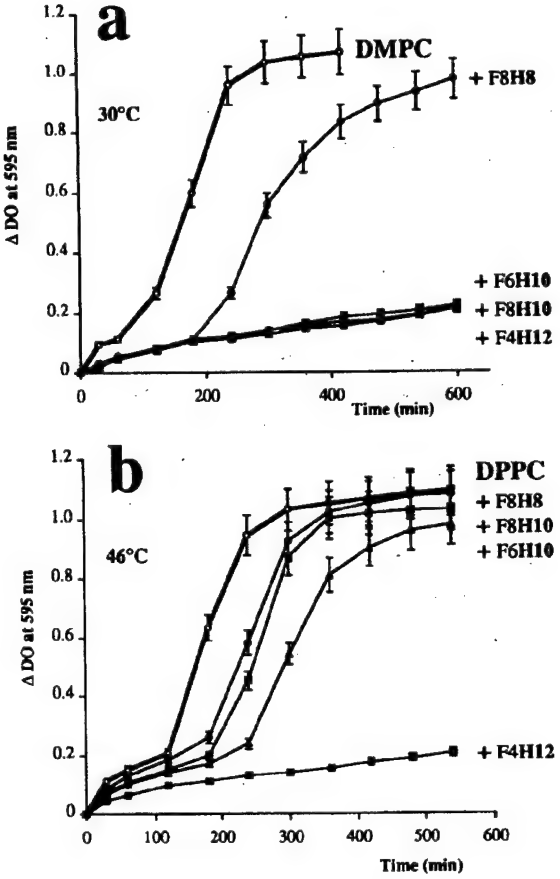


Fig 7. Incorporating fluorocarbon-hydrocarbon diblocks, $C_nF_{2n+1}C_mH_{2m+1}$ (FnHm), into vesicles made from DMPC (dimyristoylphosphatidylcholine) (**a**) or DPPC (dipalmitoylphosphatidylcholine) (**b**) results in a drastic reduction of the rate of enzymatic hydrolysis of these phospholipids by pancreatic phospholipase A_2 (as monitored by changes of absorbance of a pH indicator). From [39].

Self-aggregation of fluorinated amphiphiles

The greater hydrophobic effect developed by *F*-alkyl chains as compared to alkyl chains, combined with the above mentioned lipophobic effect, and the larger cross section and higher rigidity of the chains, result in an enhanced tendency for fluorinated amphiphiles to self-assemble. Sturdy mono and bilayers, and diverse lamellar and non-lamellar phases form at low surfactant concentrations, in water and other solvents.

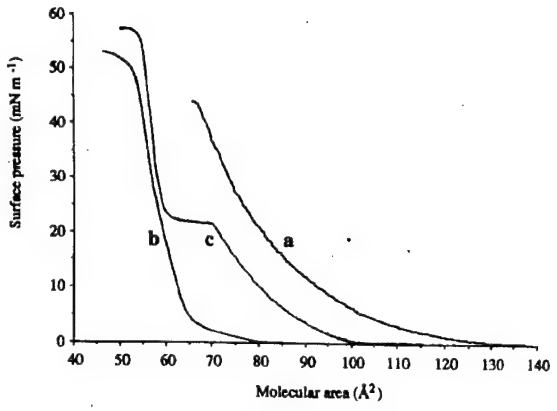


Fig 8. Compression isotherms of Langmuir monolayers made from fluorinated double-chain monomorpholinophosphates **14** (FnCmMMP, fig 5). F6C2MMP forms a liquid monolayer (a), F9C1MMP a highly organized solid monolayer (b), and F8C2MMP presents a liquid-to-solid transition (c). This indicates that increasing the degree of fluorination of the tail, while maintaining its total length constant, leads to increasing order, and that subtle changes in chain length can induce substantial modifications in the monolayer's behavior. From [67].

Langmuir films and black lipid membranes

Fluorinated amphiphiles readily form Langmuir monolayers [64]. The higher difference in energy between gauche and trans conformations, and the reduced number of kinks present in fluorinated *vs* hydrogenated chains facilitate the amphiphile's organization. Fluorinated chains have a strong tendency to orient themselves perpendicularly to the water surface due to exceedingly low chain-water interactions. This is illustrated by the fact that even a non-polar molecule, perfluoro-*n*-eicosane, $C_{20}F_{42}$, can form ordered and stable monolayers at the surface of water [65].

Further studies of monolayers made from fluorinated amphiphiles include those from Elbert *et al* [9], Barton *et al* [2] and Jacquemain *et al* [66]. Monolayers made from the single-chain phosphocholine (FnCmPC) and dimorpholinophosphate (FnCmDMP) derivatives **11** and **13** are remarkably stable, even with only ten-carbon-long hydrophobic chains such as in F9C1PC and F8C2DMP [67]. The hydrocarbon spacer inserted between the fluorinated termination and the polar head can have a definite disorganizing effect on the monolayer. In the F10CmPC series, for example, the disorder resulting from the confinement of the fluorinated and hydrocarbon segments in the same chain, as expressed by an increase of the limiting polar head area (*ie* area extrapolated at zero pressure), was found to increase when the hydrocarbon spacer increased from m = 2 to 5 ($A_\infty = 60 \pm 0.5$ and 70 ± 0.5 Å^2 for F10C2PC and F10C5PC, respectively). On the other hand, the limiting area was found to decrease for m = 11 ($A_\infty = 60 \pm 0.5$ Å^2 for F10C11PC), indicating that when the hydrocarbon spacer has reached a critical length, which was found to be about m = 5–7, chain-chain interactions may become strong enough to compensate for any induced disorder [67].

Recently, amphiphiles of type **15**, in which a *F*-alkyl segment is inserted between a hydrocarbon chain and the dimorpholinophosphate polar head, have been synthesized [68]. The study of the monolayer and self-aggregation behaviors of such 'reverse' amphiphiles is presently investigated and compared to that of 'direct' FnCmDMP amphiphiles.

Small incremental increases in fluorinated chain length can result in drastic modifications in monolayer organization and behavior. Thus, within the series of double-tailed *F*-alkylated monomorpholinophosphates **14**, F6C2MMP forms a liquid monolayer, while F8C2MMP presents an isotherm with a liquid-to-solid transition (fig 8). Increasing the Fn/Cm ratio, *ie* the degree of fluorination of the tail, while maintaining its total length constant, leads to increasing order as illustrated by the fact that F9C1MMP forms a highly organized solid monolayer, while F8C2MMP exhibits a phase transition (Goldmann *et al*, in preparation). The liquid condensed phase of both compounds is strongly organized and exhibits intense Bragg peaks when examined by grazing incidence X-ray diffraction.

Black lipid membranes (BLMs) with a perfluorinated internal film have been produced from combinations of phospholipids and fluorocarbon/hydrocarbon diblocks (Krafft *et al*, in preparation). These fluorinated BLMs turned out to be exceptionally long-lived and sturdy. Their capacitances are two to three times larger (depending on the diblock) than in the absence of diblock, and are among the highest reported to date. The thickness of the inner fluorinated core of the membrane was estimated to 20 Å in the case of F6H10 (**6**, fig 3), indicating that the fluorinated chains are not interdigitated.

Vesicles with a fluorinated bilayer membrane

The outstanding ordering and stabilizing capacity of fluorinated amphiphiles is clearly illustrated by the finding that even short single-chain *F*-alkylated phosphocholine derivatives of type **11**, upon gentle stirring, form highly stable vesicles without the need for any co-surfactant, or for any supplementary intermolecular associative interactions such as those that derive from the presence of hydrogen bonding between polar heads, ion-pairing, polymerization, diacetylenic rod-like segments, etc [69]. These vesicles even withstand heat sterilization without noticeable changes in particle size, *ie* are more stable than those obtained from standard double-tailed phospholipids. Under the same conditions, the hydrocarbon analogs of **11** ($n = 2$, m = 8), in terms of chain length (C10PC) or in terms of equivalent hydrophobicity (C15PC), only provided micelles or 3D crystals, respectively.

It is also remarkable that certain single-chain fluorosurfactants were seen to yield a diversity of self-assemblies, including small unilamellar vesicles (SUVs), multilamellar vesicles (MLVs), giant vesicles, flexible fibers and rigid tubules, whose formation and interconversion can be controlled to a certain extent by modifying the experimental conditions (fig 9) [70].

The liposomes made from the *F*-alkylated phospholipids **12** were extensively investigated. Sterilization was achieved at 120°C in standard conditions [71]. Higher gel-to-fluid transition temperatures, as compared to the hydrocarbon analogs, indicate increased ordering of the bilayer membrane [72]. Other stable, heat sterilizable fluorinated vesicles include those obtained from further examples of *F*-alkylated phospholipids [73], from various glycolipids **21** [74, 75] and glycophospholipids **23** [76]. In the latter case, the leakage rate of entrapped carboxyfluorescein was shown to depend strongly on the sugar (glucose > mannose > galactose) and decreased with increasing fluorination.

Spontaneously forming stable vesicles were recently obtained from mixtures of a perfluoropolyether surfactant and an alkylbetaine [77]. These vesicles were shown to have potential as carriers for porphyrin-based biological or biomimetic molecules.

Vesicles made from fluorinated amphiphiles are characterized by the presence of a strongly organized, adjustable fluorinated film within their bilayer membranes (fig 2a). This hydro- and lipo-phobic fluorinated membrane core confers added drug encapsulation stability as compared to hydrogenated analogs, whether in buffer or in serum [78]. The penetration/solubilization of the paramagnetic probe Tempo in the membrane of vesicles made from *F*-alkylated phospholipids **12** was shown to be suppressed when the fluorinated segment was more than four carbon atoms long [72]. The release of carboxyfluorescein entrapped in such vesicles can be significantly slowed [78]. The fluorinated membrane did not, however, prevent the active encapsulation of doxorubicin using pH or ammonium sulfate gradients [79]. The encapsulation sta-

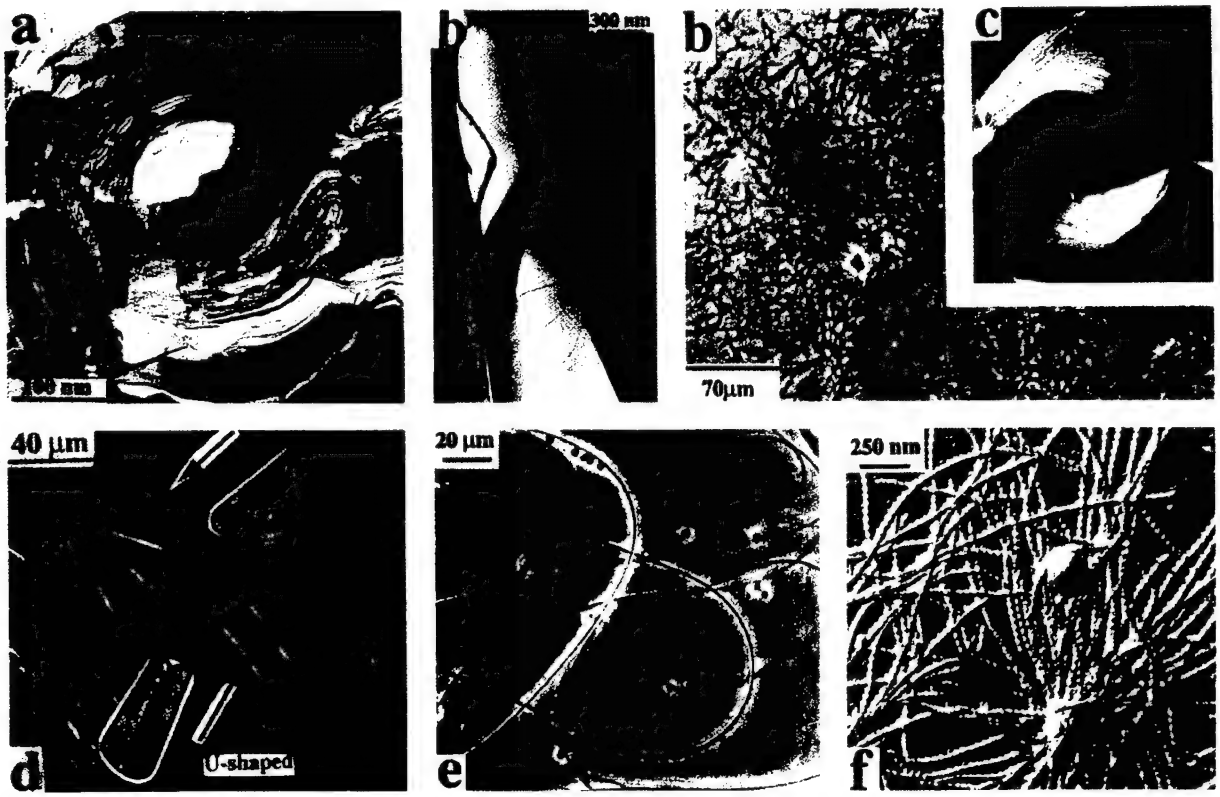


Fig 9. Fluorinated single-chain amphiphiles can yield a variety of supramolecular assemblies with diverse morphologies, while their non-fluorinated analogs only form micelles. **a.** Multilayer vesicles. **b.** Tubules. **c.** Internal aqueous core of a tubule. **d.** Twin tubules. **e.** Very long flexible tubules, all made from dimorpholinophosphates **13** (FnCmDMP). **f.** Helices made from a glycolipid of type **21.** From [26].

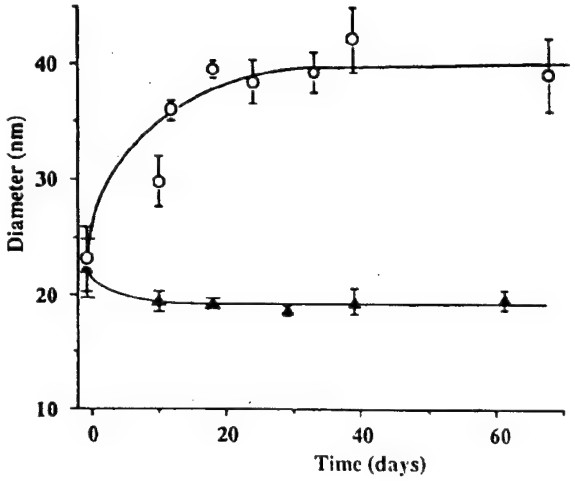


Fig 10. Evolution of DMPC and DMPC/F4H10E ($C_4F_9CH = CHC_{10}H_{21}$) (1:2) liposomes as a function of time: ○, DMPC; ▲, F4H10E/DMPC. From [38].

bility of the drug was low, presumably because of high permeability to Na^+ ions, which, after exchange with H^+, leads to an increase of the intraliposomal pH, thus favoring the release of the drug in its more diffusible neutral form.

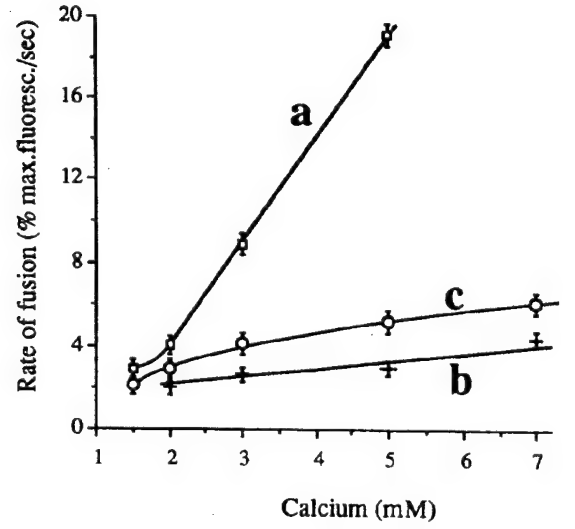


Fig 11. Initial rate of fusion (as monitored by the terbium/dipicolinic acid assay) of phosphatidylserine (PS) SUVs (a), PS/F4H10 (1:1) SUVs (b), and PS/F6H10 (1:1) SUVs (c). Vesicle fusion was induced by adding various concentrations of Ca^{2+}. The final lipid concentration was 100 μM. From [82].

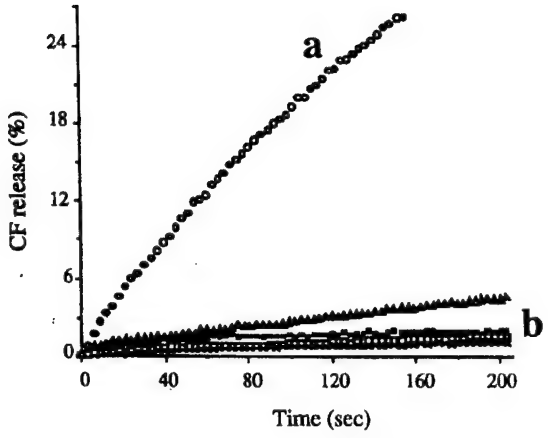


Fig 12. Comparative kinetics of 5,6-carboxyfluorescein (CF) release from phosphatidylserine (PS) SUVs (a) and PS/FnHm SUVs (b). 100% release corresponds to the fluorescence intensity measured after addition of Triton X-100 (0.1% v/v). The lipid concentration was 100 mM and the final Ca^{2+} concentration was 5.0 mM. ○, pure PS SUVs; x, F4H10/PS (1:1); ❑, F4H10/PS (2:1); ■, F6H10/PS (1:1); Δ, F8H10/PS (1:1). From [82].

Fluorinated vesicles were also obtained, at lesser expense in time and cost, by combining standard phospholipids with simple fluorocarbon-hydrocarbon diblocks such as **6** or **7** (fig 2b). Significantly greater stability and lower membrane permeability were again observed, indicating that the fluorinated segments segregate and organize tightly within the bilayer [38, 80]. Thus, vesicles made of dimyristoylphosphatidylcholine (DMPC) became heat sterilizable when two equivalents of $C_4F_9CH = CHC_{10}H_{21}$ were incorporated into their membrane; the particle size of these vesicles had not changed noticeably during sterilization or after 2 months storage at room temperature (fig 10).

The permeability of vesicles made with the single-chain phosphocholine **11** ($n = 8$, $m = 2$) was substantially reduced when diblocks of type **6** were added [81]. In this case the hydrophobicity-driven aggregation of the fluorocarbon segments of the two components results in the reconstitution of a pseudo double-tail amphiphile and in tighter packing of the membrane.

Incorporation of FnHm semi-fluorinated alkanes (**6**, $n = 4$, 6, 8 and m 10) in the membrane of SUVs made of phosphatidylserine also had an impact on the fusion kinetics of these SUVs. Fusion was induced by Ca^{2+} ions and monitored by the terbium/dipicolinic acid assay [82]. Both the rates of fusion (fig 11) and of release of the internal content of the vesicle (fig 12), as evaluated by the release of 5,6-carboxyfluorescein, were much lower for the fluorinated SUVs than for SUVs made of phosphatidylserine alone. The FnHm molecules may be dual acting by creating the internal

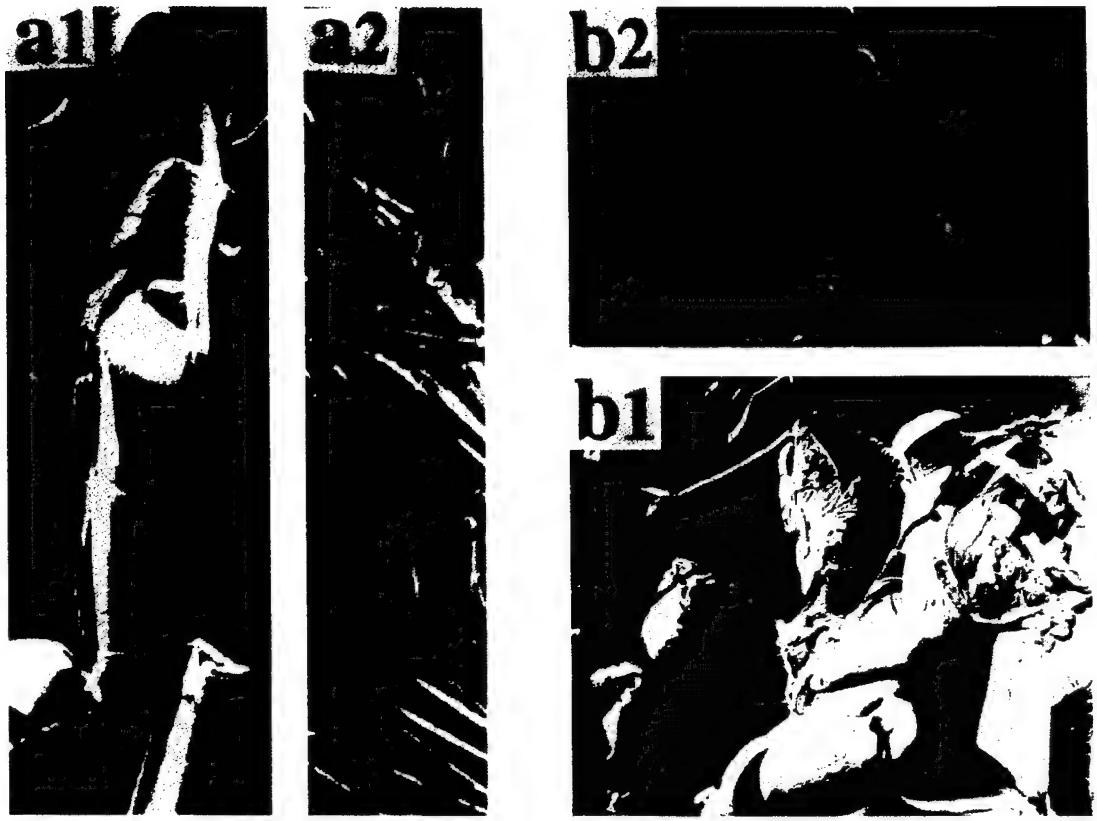


Fig 13. Tubule-vesicle interconversion. Tubules made from a mixture of single-chain dimorpholinophosphates **13** (F10C2DMP/F8C5DMP (1:1) (**a1**, freeze-fracture electron and **a2**, optical microscopies) transform into vesicles (in the gel state) (**b1**, freeze-fracture electron and **b2**, optical microscopies) when temperature is increased. Conversion is total at *ca* 40°C (Krafft *et al*, in preparation).

hydrophobic/lipophobic fluorinated film within the membrane, and by enhancing the van der Waals interactions in the hydrocarbon regions.

Polymerized fluorinated vesicles can be obtained, either by using polymerizable fluorinated amphiphiles to prepare the vesicles [83–85], or by incorporating a monomer in the lipophilic zones of a membrane made of fluorinated amphiphiles (Nakache *et al*, in preparation). In the latter case polymerization results in the formation of a double shell of polymer separated by a fluorinated film. The surfactant can subsequently be removed, leaving the intact double shell, further exemplifying the use that can be made of fluorinated amphiphiles for the microstructuration of space.

Microtubules

Hollow cylindrical microtubules made of rolled-up bilayers of amphiphiles have recently received considerable attention. The possible applications of these microtubules ranges from use as templates for the elaboration of new components for microelectronics such as vacuum field emission cathodes, or as models of natural tubules and of enzyme clefts, to microcontainers for the controlled release of active agents [86, 87]. Microtubules have been obtained from diverse dispersions of diacetylenic phospholipids [86], aldonamides [87], glutamates [88], amino acids [89], conjugated phospholipid nucleosides [90] and glycolipids [91, 92]. Cochleate lipid cylinders form when Ca^{2+} ions are added to phosphatidylserine SUVs [93]. Tubules made from a biotinylated dioctadecylamine lipid were shown to exhibit properties of molecular recognition toward the protein streptavidin which assembles spontaneously into ordered helical arrays at the tube's surface [94]. The amphiphiles utilized for the preparation of tubules all have in common the presence of a chiral center and often also the capacity of forming hydrogen bonds between their polar heads. The chiral center was deemed necessary for the inception of the rolling-up process which leads to the tubular structures.

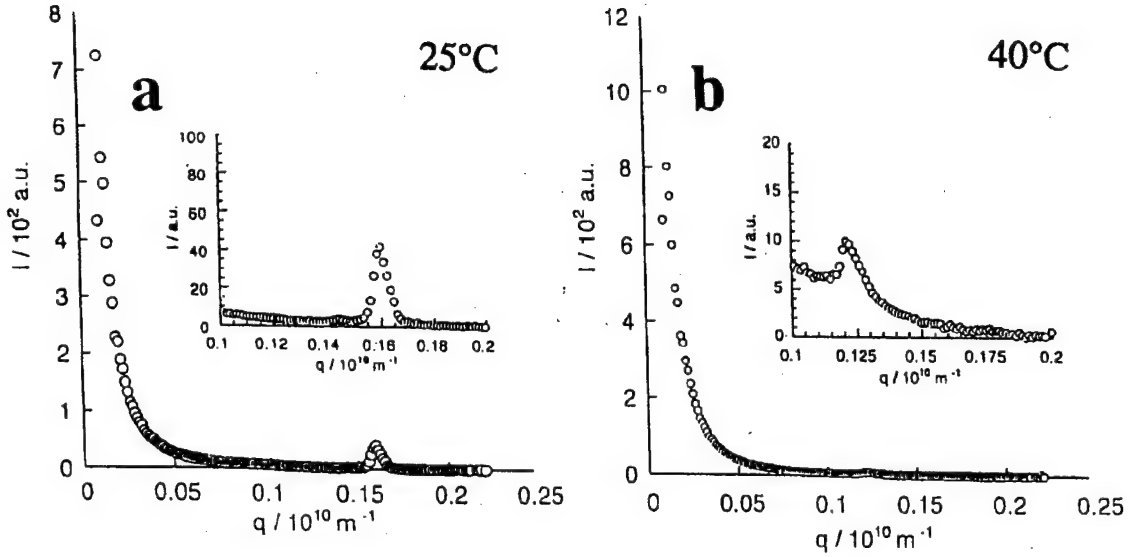


Fig 14. Small angle X-ray diffraction monitoring of the conversion of tubules (at 25°C) into vesicles (at 40°C) in dispersions of a mixture of single-chain dimorpholinophosphates **13** (F10C2DMP/F8C5DMP, 1:1). The repeating distance within bilayers is smaller in tubules (39 Å) than in vesicles (52 Å). From [96].

We found that microtubules could also be obtained from non-chiral, non-hydrogen bound, single-chain fluorinated amphiphiles such as **13** (fig 9) [95]. The aqueous internal channel visible on the electron micrographs was confirmed by epifluorescence microscopy after carboxyfluorescein had been incorporated. The fact that hydrocarbon analogs of **13** only form micelles further demonstrates the powerful structuring effect of the fluorinated moieties.

Tubules are generally considered as being more organized than vesicles. The tubules made of **13** actually convert into vesicles when heated (fig 13). Small angle X-ray diffraction measurements showed that the repeating distance in the bilayers was smaller in the microtubules (visualized by optical and electron microscopies at 25°C) than in the vesicles which had formed at 40°C (fig 14) [96]. The latter slowly convert back into tubules upon cooling. The tubules of **13** are exceptionally sturdy; they can be centrifuged, dried, stored, and resuspended in a solvent without noticeable alteration of their morphology. Changes in the amphiphile's molecular structure or in the tubules' preparation conditions allow adjustment of tubule length and diameter in a reproducible fashion (Giulieri *et al*, in preparation). Fluorinated tubules were also grown in organic solvents such as dimethylsulfoxide and dimethylformamide [97]. Other tubular self-aggregates have been made by co-dispersing a *F*-alkylated phosphocholine of type **11** with a *F*-alkylated alcohol such as $C_8F_{17}C_2H_4OH$ [98].

The mechanism of formation and evolution of tubules has been unraveled using optical and electron microscopy. In the case of tubules of F10C2DMP, monitoring in real time the various steps of their formation was possible in dimethylformamide (Giulieri *et al*, in preparation). Formation of tubules was seen to involve the aggregation and fusion of vesicles to yield flat multibilayer sheets; these sheets were then observed to roll-up from opposite sides to form twin cylindrical microstructures, which eventually separate into isolated tubules. Depending on the amphiphile, tubules retain their morphology for many months, or collapse and expel the solvent present in the inner core, eventually yielding crystalline needles [98].

Additional tubules were obtained from anionic double-tailed glucolipids of type **22** (fig 15) [99]. The formation of these tubules is pH-dependent, indicating that the formation of hydrogen bonds between the phosphate group and a hydroxyl group of the sugar is likely to be involved. At a high pH, the polar heads of the amphiphiles are less hydrated and tubule formation is favored over vesicle formation. Both the partly-fluorinated glucophospholipid **22** and its fully hydrogenated analog form tubules. Introducing one fluorinated chain allows the vesicle-tubule transition to occur above room temperature; it also has a significant impact on tubule diameter which becomes five to ten times smaller, reaching values of 300 nm. The structure of fluorinated tubules has been studied by electron microscopy, small angle X-ray and neutron scattering experiments [96].

Fig 15. Tubules formed from a mixed-chain fluorocarbon/hydrocarbon glucophospholipid **22** as observed by cryo-transmission electron microscopy (**a**) (note the internal aqueous core) (from [96]), and by negative staining (**b**) (from [99]).

Colloidal systems with a fluorocarbon phase

Obtaining stable fluorocarbon emulsions

An extensive range of direct, reverse and multiple emulsions, gel-emulsions and microemulsions with a fluorocarbon phase have been reported (fig 6). Achieving stability is a stringent requirement for these emulsions' usefulness and commercial viability. Insufficient stability downed the first fluorocarbon emulsion for oxygen delivery that was approved by the United States Food and Drug Administration in 1989. This emulsion (Fluosol®, Green Cross Corp) had to be stored and shipped frozen and required a cumbersome reconstitution procedure prior to administration [100]. The presently developed, ready-for-use product, Oxygent™ (Alliance Pharmaceutical Corp, San Diego, USA), associates a somewhat lipophilic fluorocarbon, perfluorooctyl bromide, **1**, with egg yolk phospholipids [4, 48]. Molecular diffusion, the principal cause of particle size increase in submicronic fluorocarbon emulsions, is counteracted by adding small amounts of a higher homologue of perfluorooctyl bromide, perfluorodecyl bromide, **2**, which reduces the solubility and diffusibility of the fluorocarbon phase in water [101]. Perfluorotripropylamine, **4**, and perfluoro-*N*-methylcyclohexylpiperidine, **5**, were used for the same purpose in Fluosol and Perftoran, a Russian preparation [102], respectively; these compounds being non-lipophilic have, however, much longer organ retention times. Preserving small particle sizes is also indispensable for achieving effective intravascular persistence and to reduce side-effects related to phagocytosis and macrophage activation [4, 103].

Another highly effective means to stabilize fluorocarbon-in-water emulsions and to control their particle size distribution is to supplement standard phospholipids with

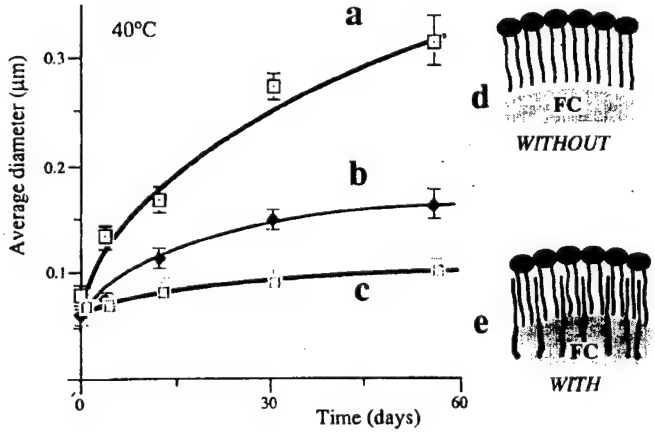


Fig 16. Particle size increase at 40°C in a fluorocarbon/phospholipid emulsion (90% w/v perfluorooctyl bromide; 4% w/v egg-yolk phospholipids (EYP)), emulsified with EYP alone (a); stabilized with equimolar amounts of EYP and $C_{16}F_{34}$ (b); stabilized with equimolar amounts of EYP and $C_6F_{13}C_{10}H_{21}$(c). $C_{16}F_{34}$ and $C_6F_{13}C_{10}H_{21}$ have close to identical boiling points and should have comparable molecular diffusion-prevention effects according to the Lifshitz-Slezov equation [4]. Hypothetical 'dowel effect' of a mixed fluorocarbon-hydrocarbon diblock compound at the fluorocarbon-phospholipid film interface [36]: without (d), and with $C_6F_{13}C_{10}H_{21}$ (e). From [36, 106].

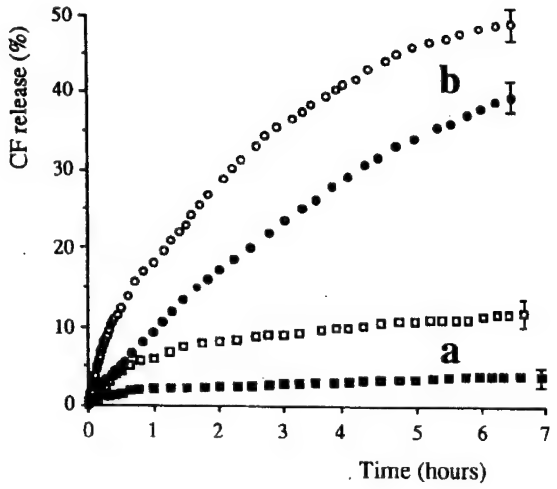


Fig 17. Release of 5,6-carboxyfluorescein encapsulated in the internal water droplets of water-in-fluorocarbon reverse emulsions (a) and water-in-hydrocarbon reverse emulsions (b). ■, Perfluorooctyl bromide/fluorinated dimorpholinophosphate **13** (F8C11DMP); ❑, perfluorooctylethane/F8C11DMP; ●, octyl bromide/Span 80; ○, isopropyl myristate/Span 80. Fluorocarbons, which constitute a barrier to the diffusion of the hydrophilic probe, can help control the release of content. From [108].

mixed fluorocarbon-hydrocarbon diblock compounds such as **6** or **7** [36]. The diblock compounds are believed to concentrate primarily at the interface between the fluorocarbon droplets and the film of phospholipids that surrounds them (fig 16), acting as molecular 'dowels' at this interface [104–106]. A clean room equipped with high pressure homogenizers has been built at the Institut Charles Sadron, which allows the preparation of emulsions of this type, taylor-made for biomedical research.

Reverse and multiple emulsions

Reverse, water-in-fluorocarbon emulsions have also been devised. The challenge was to stabilize dispersions of water in one of the most hydrophobic media that exists. In addition, molecular diffusion of water in the fluorocarbon phase, which leads to Ostvald ripening, is facilitated by the extremely low intermolecular cohesion of liquid fluorocarbons. Very stable reverse emulsions were eventually obtained using the highly fluorophilic neutral surfactant **13** (n = 8, m = 11) [107]. Further stability was gained by adding a salt to the aqueous internal phase. A range of drugs, including antibacterials, bronchodilators, mucolytic, tuberculostatic, cholinergic and antineoplastic agents, etc, were incorporated in these emulsions without loss of stability. Release of 5,6-carboxyfluorescein from such emulsions was shown to be much slower than from water-in-hydrocarbon oil emulsions (fig 17) [108].

Totally apolar hydrocarbon-in-fluorocarbon emulsions, which may be useful for the delivery and controlled release of lipidic materials, have now also been obtained. The amphiphile used to prepare and stabilize such totally apolar emulsions consists again in simple semi-fluorinated alkanes of the FnHm type [37].

These direct and reverse emulsions also led to a range of multiple emulsions, including some novel combinations that involve three distinct non-miscible phases: a fluorocarbon, a hydrocarbon and water (fig 18) [109, 110]. For example, an internal hydrocarbon phase can be separated from the continuous fluorocarbon medium by an intermediate aqueous phase; both lipophilic and hydrophilic drugs may be loaded in such multicompartment systems.

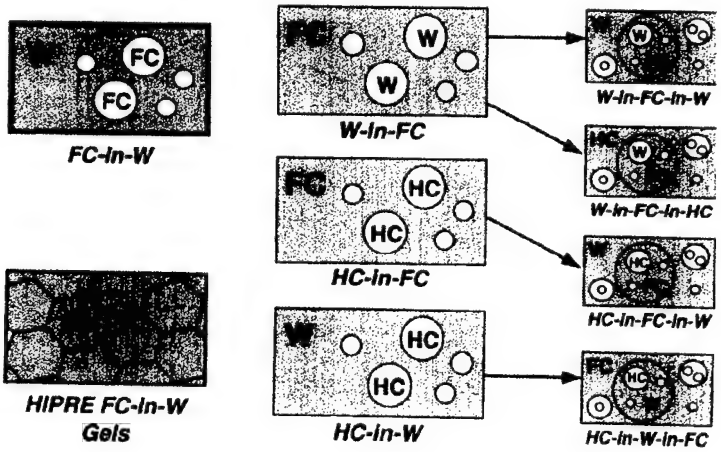


Fig 18. Direct and reverse fluorocarbon emulsions lead to a variety of multiple emulsions, some of which may involve three non-miscible phases: a fluorocarbon, a hydrocarbon, and water.

Fluorocarbon gels

Gelifying fluorocarbons has been another serious challenge. Fluorocarbons are indeed extremely fluid, mobile liquids with very weak cohesive forces, and they do not dissolve the usual gelifying agents. Nevertheless several types of gels have been reported [111]. Some of these gels are very rich in water and consist of a dispersion of water droplets in an external phase which is actually a water-in-fluorocarbon microemulsion; the surfactants used were perfluoroalkylated ethoxylated alcohols [112, 113].

On the other end of the composition spectrum, stable rigid and transparent gels containing up to 99% fluorocarbon could be prepared from a range of fluorocarbons with a wide spectrum of boiling points, using a very low amount of the perfluoroalkylated amine oxide **26** as the surfactant [114]. These gels consist of a high internal phase ratio fluorocarbon-in-water emulsion and have a compartmentalized structure with polyhedral fluorocarbon domains separated by a reverse, hydrated film of surfactant (fig 19). Another type of fluorocarbon-rich gels, in which the fluorocarbon is the continuous phase, were obtained by dispersing a mixture of phospholipids and fluorocarbon-hydrocarbon diblocks in the fluorocarbon, and then adding small amounts of water. Rapid gelification occurs, which is believed to be due to the formation and rapid growth of long, worm-like entangled micelles of surfactants [115].

Examples of applications in the biomedical field

Tools for biomedical research

Few studies on the use of fluorosurfactants for protein extraction have been reported to date. Although fluorinated chains augment surface activity, fluorinated amphiphiles appear to be less detergent toward membranes than their hydrogenated counterparts. This was already indicated by lesser hemolytic activity. Lower protein solubilization potency was observed for compound **17** ($R_F = C_{10}F_{21}$, $P = 4$), in comparison to its hydrocarbon analog or to Triton X-100 [116]. An early claim according to which the phosphocholine derivative **11** ($n = 8$, m = 2) could extract a flavoprotein-cytochrome b_{558} complex without denaturation [117] was not substantiated by further studies [118]. The data available so far thus indicate that fluorinated surfactants are only poorly or not effective for protein extraction.

An astute molecular device, **28**, was built that takes advantage of the tendency of fluorocarbon segments to cluster, in order to create separate zones in which to confine moieties which belong to the same molecule and have distinct functions [119]. Compound **28** is destined to function as a protein recognition device and has an internal *F*-alkylated segment that separates a lipophilic retinoid ligand from a lipidic tail. The fluorocarbon film that forms by aggregation of the *F*-alkyl segments keeps the ligand exposed

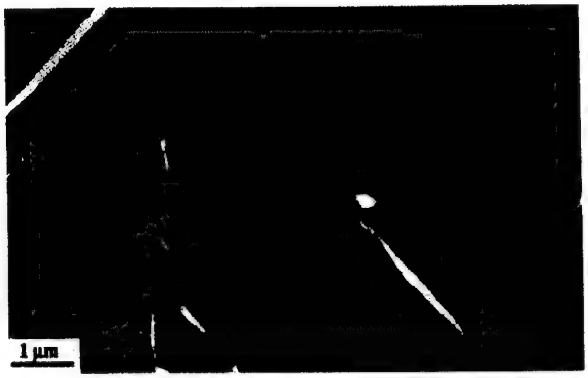
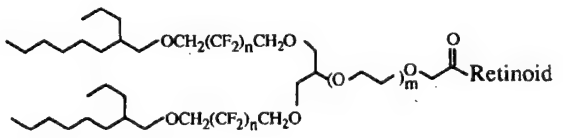


Fig 19. Freeze fracture transmission electron micrograph of a high internal phase ratio (98.5%) emulsion of a fluorocarbon (APF-260, Air Products) in water, showing the polyhedric liquid foam domains (micrograph: T Gulik Krzywicki). The surfactant utilized is the fluorinated amine oxide **26**. The emulsion presents itself as a stable, transparent viscoelastic gel. From [114].

on the aqueous side of a monolayer of the amphiphile and prevents it from being buried in the lipid region of the monolayer. Incubation with a retinoid receptor showed that the macromolecule was efficiently and specifically bound and concentrated onto the lipid film, which was not the case when a non-fluorinated analog of **28** was used (scheme 1).

Gel-like network structures with well-defined mesh size were obtained from fluorocarbon-tailed polyethylene glycols. These gels were used for electrophoretic DNA sequencing in capillary columns [120]. A fluorocarbon affinity emulsion was produced by derivatization with affinity ligands of an *in situ* cross-linked poly (vinylalcohol) emulsifier and used for the extraction of human serum albumin from plasma, or of glucose-6-phosphate dehydrogenase from homogenized baker's yeast [121].

In vitro DNA transfection efficacy was not significantly affected when lipospermines with fluorinated lipid tail ends, rather than hydrocarbon ends, were used. This provides evidence indicating that cationic lipid mixing with cellular lipids may not be an important part of the gene transfer process [122]. In another approach a neat fluorocarbon was used for achieving homogenous delivery of a gene-loaded adenoviral vector to the lungs of rabbits [123]. Both gene expression and gene expression distribution throughout the lungs were improved as compared to a saline control.



Scheme 1. Structure **28**.

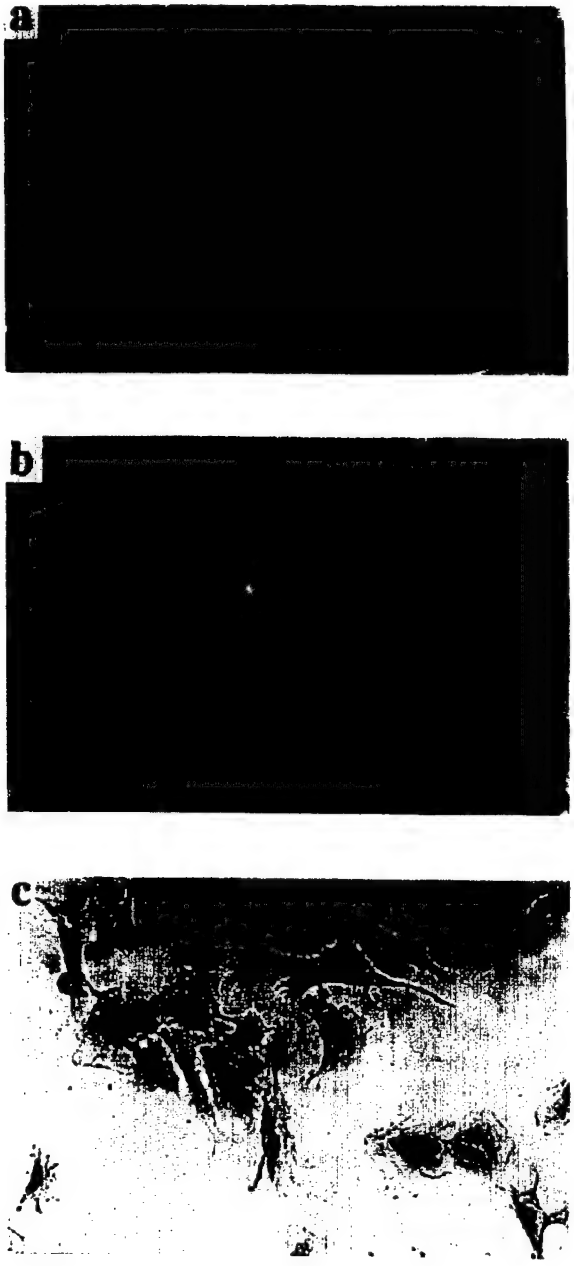


Fig 20. Cultured human endothelial cells incubated with a fluorocarbon emulsion stabilized by mixed fluorocarbon-hydrocarbon diblocks (**a**); no cytotoxicity was observed with regards to controls (**b**). On the other hand, the usual UW (University of Wisconsin) organ preservation solution was toxic to cells (**c**). From [126].

Fluorocarbons have been utilized for improving and regulating oxygen supply and pH (through CO_2 delivery) in a variety of cell cultures [124]. Normal cell division and increase in cell density were reported. Mechanical damage caused to cells can be reduced by stirring the culture through the underlying fluorocarbon phase [125]. Protection of alveolar cells against destruction by activated polymorphonuclear granulocytes was noted when the cells were grown on an oxygenated layer of perfluorooctyl bromide [126]. Cell cultures have also been utilized to assess the toxicity of crude fluorocarbons and monitor their purification [127, 128].

Tissue and organ preservation is also currently being investigated. Fluorocarbon emulsions can help prolong the viability of isolated tissue- and organ-based models utilized in physiological studies, including in normothermic conditions. Embryonic chick heart tissue was grown on a fluorocarbon-supplemented medium [129]. An oxygenated perfluorooctyl bromide emulsion was more effective than a suspension of fresh bovine erythrocytes in preserving an *in vitro* preparation of the rat small intestine [130]. Aerobic normothermic preservation of blocks of organs, comprising heart-lung, liver, pancreas, kidney and small intestine was achieved [131]. A fluorocarbon emulsion-perfused pig kidney model allowed investigation of the xenogenic cellular rejection that occurs when the kidneys are perfused with human peripheral blood lymphocytes [132]. The emulsions were of the diblock-stabilized type [36]. The effect of such fluorocarbon emulsions on cultured human endothelial cells was investigated as a preliminary step to achieving warm organ preservation [133]. It was found that the fluorocarbon emulsions were devoid of cytotoxicity. By contrast, the classical organ preservation solutions, UW (University of Wisconsin) and EC (Eurocollins), were toxic to the cells, probably due to their high K^+ concentrations (fig 20).

The diblock-stabilized fluorocarbon emulsions that allowed reproducible, stable preservation of the intestine's neurogenic motor pattern (known as the most sensitive to hypoxia) [130], were recently used to perfuse intestinal preparations of mice in which a gene depletion had been induced (knockout mice) (Bouley L *et al*, in preparation). This model may be useful for the investigation of certain diseases of the central nervous system such as porphyry. It has also potential in pharmaceutical research for the screening of drugs.

Therapeutic oxygen delivery

One of the major fluorocarbon-based products under clinical development is an injectable fluorocarbon-in-water emulsion for delivering oxygen to patients at risk of tissue hypoxia [43–48]. Recently completed Phase II clinical trials with Oxygent™ demonstrated that the product, when used in conjunction with acute normovolemic hemodilution during surgery, was more effective than blood in reversing transfusion triggers, and delayed the need for a subsequent transfusion significantly longer than blood [134]. Another

fluorocarbon emulsion (Perftoran®, Perftoran Co, Puschino, Russia) has been approved for use in Russia [102]. An emulsion based on α,ω-dichloroperfluorooctane **3** (fig 1), Oxyfluor (Hemagen-PFC, St Louis), is in early clinical trials [135].

Using such emulsions as a delivery system for oxygen also shows potential for protecting tissues during transient anemia resulting from trauma; when blood flow is restricted during conditions such as myocardial infarction or stroke; for use during cardiopulmonary bypass surgery [136]; to prevent reperfusion injury; to improve oxygen delivery to certain tumors, rendering these tumors more responsive to radiation and chemotherapy, etc [4, 43–46, 137, 138].

A neat fluorocarbon (Liquivent®, Alliance Pharmaceutical Corp) is currently being clinically evaluated for treatment of respiratory distress through liquid ventilation [49, 50]. The fluid and effectively spreading, O_2/CO_2-carrying liquid, reduces a patient's exposure to the harmful effects of conventional mechanical ventilation and helps to recruit collapsed alveoli, improving both lung compliance and oxygenation.

Contrast agents for diagnosis

Fluorocarbons provide the first effective (*ie* stable-enough in the circulation) contrast agent for ultrasound imaging. One such agent, Optison™ (Molecular Biosystems Inc, San Diego, CA), which consists in microbubbles of perfluoropentane within an albumin shell [139], has just been approved for use in the United States (December 1997). Several more products are in advanced clinical trials. MRX-115 (ImaRx Pharmaceutical Corp, Tucson, AZ) is made of lipid encapsulated perfluoropentane [140]. Another agent, Echogen® (Sonus Pharmaceuticals, Bothel, WA), is an emulsion of perfluoropentane whose droplets convert, upon activation, into gas bubbles at body temperature [141]. It is noteworthy that this emulsion is stabilized using a fluorosurfactant, which is, as far as we know, the first intravascular use of a fluorosurfactant in humans. Still another product, Imagent® US (Alliance/Schering AG, Berlin, Germany), takes advantage of the very low solubility of fluorocarbons in water to osmotically stabilize micron-size gas bubbles using perfluorohexane [142]. When injected in the vasculature, these microbubbles function as reflectors for ultrasound, allowing, for example, the assessment of cardiac function, diagnosis of perfusion abnormalities, and detection of tumors in organs [143].

Externally applied fluorocarbon-filled pads (SatPad® Alliance Pharmaceutical Co, San Diego, USA) are now commercially available which improve magnetic resonance (MR) image quality by increasing magnetic homogeneity when fat saturation techniques are utilized [144]. A fluorocarbon has been approved in the United States for oral use as a bowel marker for MR imaging; in this case it is the absence of signal which creates the desired contrast [145].

Drug delivery and miscellaneous uses of fluorocarbons and highly fluorinated systems

A variety of neat fluorocarbons, including perfluorodecalin, perfluorooctyl bromide, perfluoroperhydrophenanthrene and the diblock **8**, are being used in ophthalmology as a tamponade to manage complicated retinal detachments [146–149]. As indicated earlier, fluorinated vesicles and other self-assemblies of fluorosurfactants, and emulsions, gel-emulsions and multiple emulsions with a fluorocarbon phase offer a range of multicompartmentalized vehicles that may be useful for drug delivery [25–31].

Fluorinated surfactants may play a unique role as formulating agents when extreme surface activity, high fluorophilicity, or resistance to an aggressive biological environment is required. Covalently grafting a cleavable fluorocarbon chain onto a drug promotes the self-assembly of the resulting amphiphile or its incorporation into a vesicular membrane, and may help controlling the targeting and delivery of the drug. Bioactive molecules, targeting devices and markers can, for example, be grafted simultaneously onto small amphiphilic telomers [150]. The *F*-alkyl chain enhances the self-aggregation of the prodrug. The amphiphiles' polar head can obviously play a role in targeting. Glycolipidic fluorosurfactants may, for example, be used to achieve targeting through specific recognition by membrane lectins of carbohydrates arranged at the surface of vesicles. The use of fluorosurfactants for stabilizing micronized inhalation drug suspensions for metered drug inhaler has been proposed [151, 152]. Fluorosurfactants also made possible the preparation of microemulsions of water in a supercritical CO_2 continuous phase [153, 154].

Perspectives

The potential of fluorocarbons in the biomedical field appears to be well established. Fluorocarbons are uniquely suited for the formulation and *in vivo* transport of oxygen and carbon dioxide; these transport properties could also be applied to other gases such as nitric oxide. Other products for therapeutic and diagnostic uses, that depend on physical characteristics or combinations of characteristics specific to fluorocarbons, are being developed or investigated. Further applications are likely to emerge that will take advantage of these features.

Water-in-fluorocarbon emulsions, lipid-in-fluorocarbon emulsions and multiple emulsions with a fluorocarbon continuous phase have potential for use in pulmonary drug delivery. This application represents a logical extension of the use of fluorocarbons in liquid ventilation. The reverse emulsions should allow uniform and reproducible distribution of active agents throughout the lung, including the dependent regions, and may provide improved control over drug release. Fluorocarbon gels can provide very thin, water- and fat-repellent, gas-permeable films that may find topical ap-

plications as wound healing ointments, protective barrier creams, as well as use in cosmetics.

The incorporation of a fluorocarbon chain in a molecule can drive the amphiphilic character of this molecule to extremes, resulting in surface activities that cannot be attained with non-fluorinated fatty tails. Fluorosurfactants may therefore find uses wherever surface chemistry is critical. Because of considerably higher effectiveness and efficiency, fluorosurfactants can usually be used in far smaller quantities than standard, non-fluorinated surfactants. This can result in favorable efficacy/toxicity ratios, which may offset the fluorosurfactants' higher cost.

Fluorosurfactants offer the ultimate in terms of hydrophobic effect, which provides potent driving forces for such amphiphiles to self-assemble into supramolecular constructs. The fact that, in addition to being hydrophobic, *F*-alkyl chains are lipophobic is a unique attribute that has been barely exploited. Fluorosurfactants can provide building blocks of supramolecular constructs when extreme segregation between distinct domains (hydrophilic and lipophilic, or both hydrophilic, or both lipophilic) is desired. They provide an additional tool for the chemist for programming the 'self'-assembling of molecules.

Generally speaking, fluorinated amphiphiles constitute novel, versatile components useful for preparing films and membranes; elaborating and stabilizing colloidal systems; coating and dispersing micro- and nano-particles; protecting large bioengineered molecules; modulating the response of temperature and pH-sensitive materials, etc.

Self-association of fluorosurfactants in discrete objects, such as vesicles and tubules, occurs with molecules that are often structurally simpler (shorter, single-tailed, non-chiral, non-hydrogen-bonding) than in the hydrocarbon series. This should facilitate the establishment of structure/property relations, and the elucidation and understanding of the role of individual contributors to a given self-association phenomenon.

The fact that stable organization of fluorinated amphiphiles, especially at interfaces, can be achieved for significantly shorter chain length than for hydrocarbon analogs, should open the access to thinner, yet stable. Langmuir and Langmuir-Blodget films, and membranes.

Building a fluorinated film within a bilayer membrane has a number of interesting consequences that remain to be exploited. Not only can this film strongly stabilize the membrane, but it can also impact on phase transitions, modify the membrane's curvature, reduce the membrane's permeability to both hydrophilic and lipophilic agents, and influence the behavior of a particle in a biological environment. The fact that little energy is usually needed to induce the formation of fluorinated vesicles may be an advantage when the material to be encapsulated is fragile. The observation that the internal fluorinated film can affect the *in vivo* recognition of particles or the enzymatic attack of the membrane is intriguing and deserves further investigation.

Fluorinated vesicles are usually less permeant to entrapped materials than hydrocarbon vesicles. They may be used for targeting and delivering drugs, prodrugs, contrast agents, immunoactive material, genetic material, etc. They may, as needed, be fitted with markers and targeting devices, or rendered pH-, pressure- or temperature-sensitive.

Fluorosurfactants also allow the preparation of a variety of stable, dispersed, micro- and nano-compartmentalized systems with a fluorocarbon phase, such as emulsions, microemulsions, multiple emulsions, etc. Colloidal systems with three distinct, immiscible phases can be made.

In addition to use as drug delivery devices, such systems could find uses as templates for the elaboration, possibly after polymerization or metallization, of new microporous or microcompartmentalized materials useful as controlled-release systems for other materials, as catalysers, molecular sieves, new composite materials for use in electrooptics and microelectronics. In polymerization chemistry they may provide a means of separating, at the nanometer level, zones that need to be polymerized separately.

The analogy that exists between fluorocarbons and gases, as a consequence of low van der Waals forces, could be further exploited, as for preparing dispersed systems in supercritical fluids and, in particular, in CO_2. Fluorosurfactants are likely to be indispensable for ensuring the stability of such dispersions.

The simple mixed fluorocarbon-hydrocarbon diblock amphiphiles should find novel uses in colloid chemistry. Fluorocarbon-in-water emulsion stabilization using FnHm diblocks may provide the basis for a future generation of injectable oxygen carriers. Such emulsions are valuable in biomedical research, for example for stabilizing and extending the viability of experimental models based on isolated tissues and organs. They could allow warm storage of organs destined for transplantation, thus preventing damage resulting from reoxygenation after hypoxia.

The ability of the FnHm diblocks to combine with standard hydrogenated amphiphiles, particularly phospholipids, and improve their performances, strengthen bilayer membranes, and modulate their properties, is attractive. Further exploration of their membrane ordering and stabilizing capacity should undoubtedly be pursued. The diblocks have the advantage over regular fluorosurfactants of being easy to synthesize and should present a simplified pharmacology.

In contrast to fluorocarbons, the pharmacology of fluorosurfactants is still in its infancy. The available, though limited, preliminary acute toxicity data are encouraging. The spectacular reduction or suppression of hemolysis when fluorinated chains are introduced in surfactants, is remarkable. Absorption, distribution, metabolism and excretion studies are badly needed. The diversity of recently synthesized, well-defined fluorosurfactants should facilitate this task. The results of these studies will largely determine the extent to which fluorosurfactants may be used in pharmaceuticals; the acceptable level of side effects will of

course also depend on the indication, dose, and route and regimen of administration.

The limited information available on membrane protein extraction using fluorosurfactants indicates lesser effectiveness than for hydrocarbon surfactants or no effectiveness at all, probably due to the lipophobic character of the perfluoroalkyl tails.

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MULTICOMPARTMENT MICELLES BASED ON HYDROCARBON AND FLUOROCARBON POLYMERISABLE SURFACTANTS

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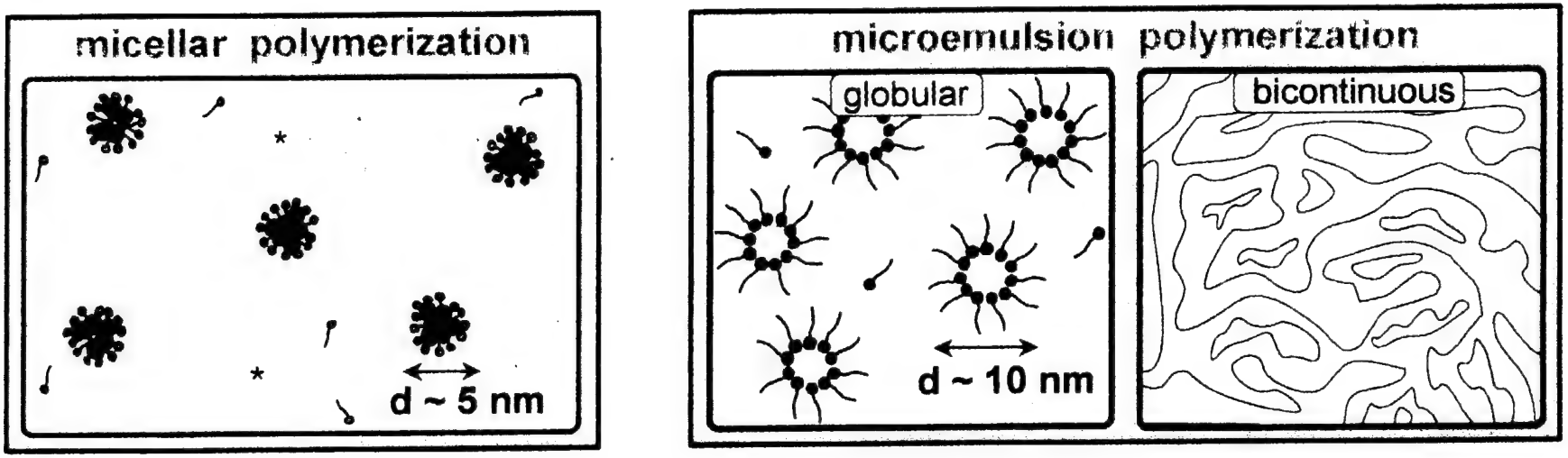
Polymers that form micelle-like structures are of particular interest for biological and pharmaceutical applications. They may be used in drug delivery processes due to their ability to solubilize hydrophobic compounds and to an improved stability when compared to their low molecular weight amphiphilic counter-parts.

One way to synthesize these polysoaps is a free radical polymerization of monomeric surfactants (surfmers) or the copolymerization of these surfactants with hydrophilic monomers in aqueous micellar media. In the latter case, the polymer structure is similar to a string of beads where the beads are the covalently linked hydrophobic microdomains distributed along the hydrophilic backbone string. In the present study we have investigated the possibility of synthesizing polymers formed of hydrophobic microdomains of different nature and connected by hydrophilic linear spacers. Such systems could be of particular interest for the specific solubilization of mutually incompatible hydrophobic compounds in controlled drug release.

The synthesis of multicompartment polymeric micelles (MCPM) was achieved by aqueous radical terpolymerization of a water-soluble monomer (acrylamide) with both hydrocarbon (H) and fluorocarbon (F) surfmers in the micellar state. The selected H- and F-surfmers are $CH_2 = CH\text{-}CON(C_2H_5)\text{-}CH_2\text{-}CH_2\text{-}N(CH_3)_2\text{-}CH_2COOC_{16}H_{33}/Br/Cl$ and $CH_2 = CH\text{-}CONH\text{-}CH_2\text{-}CH_2\text{-}N(CH_3)_2\text{-}CH_2COOCH_2CH_2\text{-}C_8F_{17}/Br$, respectively. Their mutual incompatibility in aqueous solution was checked by conductivity and surface tension experiments. Two cmc values are found, in favor of the coexistence of two distinct types of micelles at surfactant concentrations above 1 mmol/L (second cmc) over a broad composition range. The solubilization properties of the pure and mixed surfactant systems were studied for different hydrophobic probes. Significant differences in the solubilization capacity occur due to the nature of the dye, of the surfactant and of the micelle shape and composition. A kinetic study on the incorporation behavior of the H- and F- surfmers in the polyacrylamide backbone during a batch polymerization shows a compositional drift as a function of conversion which is attributed to micellar effects. A semi-continuous process was designed which allows the synthesis of copolymers homogeneous in composition. The presence of well segregated H- and F- microdomains in terpolymers could be inferred from viscosity and fluorescence experiments.

FREE-RADICAL POLYMERIZATION in NANOSTRUCTURED MEDIA



- large overall interfacial area
- microenvironment effect (polarity)

→ polymeric materials with *specific properties* and *morphologies*

HYDROPHOBICALLY MODIFIED WATER-SOLUBLE POLYMERS

⇩

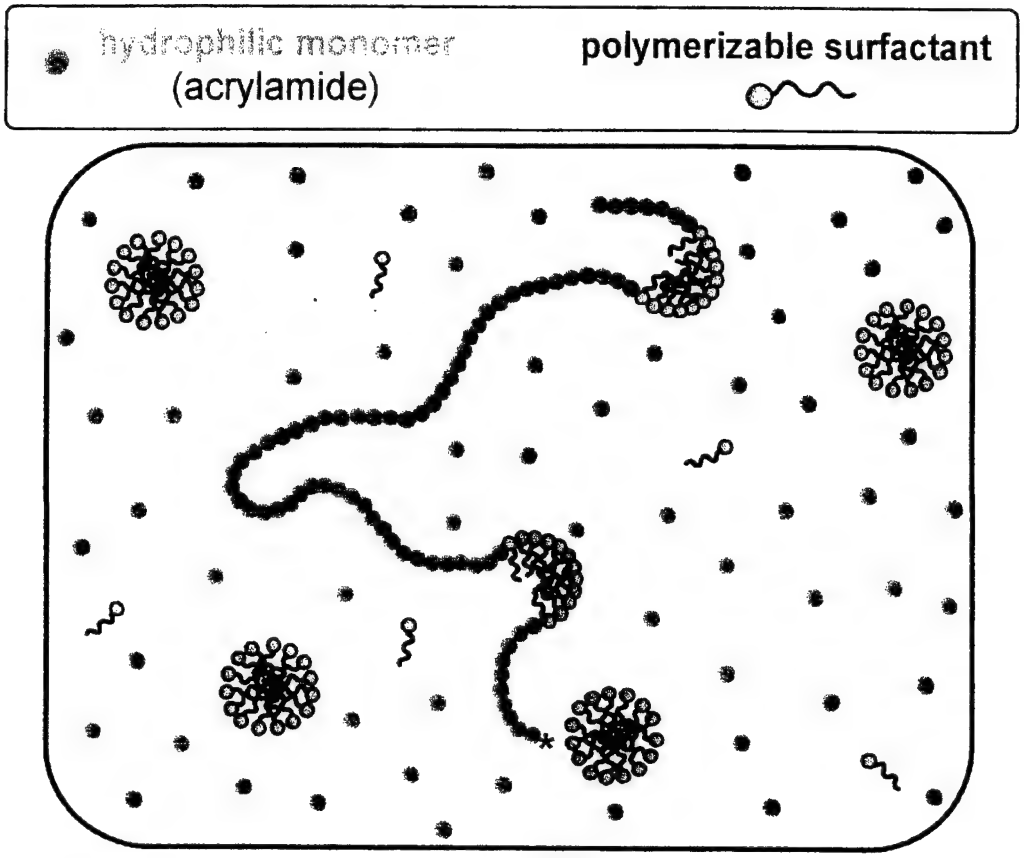
tuning aqueous solution properties
via *inter-* and/or *intra-molecular associations*

⇩

multicompartment [illegible] micelles

radical copolymerization in aqueous micellar media

D. Renoux (Thesis 1995)
J. Selb, F.C. (*ACS Symp. Ser.*, in press)



water-soluble main monomer (97-99 mol%)

+

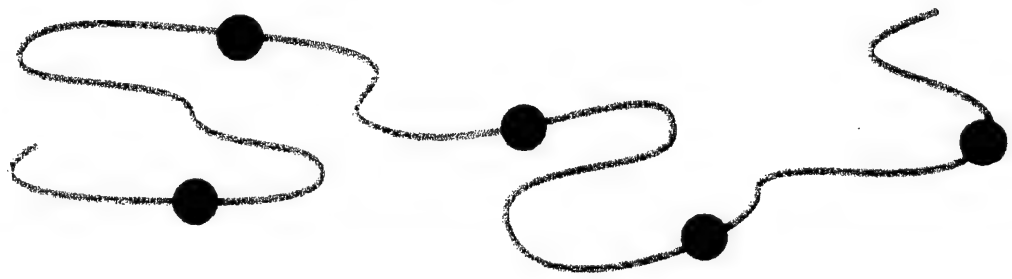
micelle-forming monomer (1-3 mol%)
(C >> cmc, aggregation number : ~50)

⇩

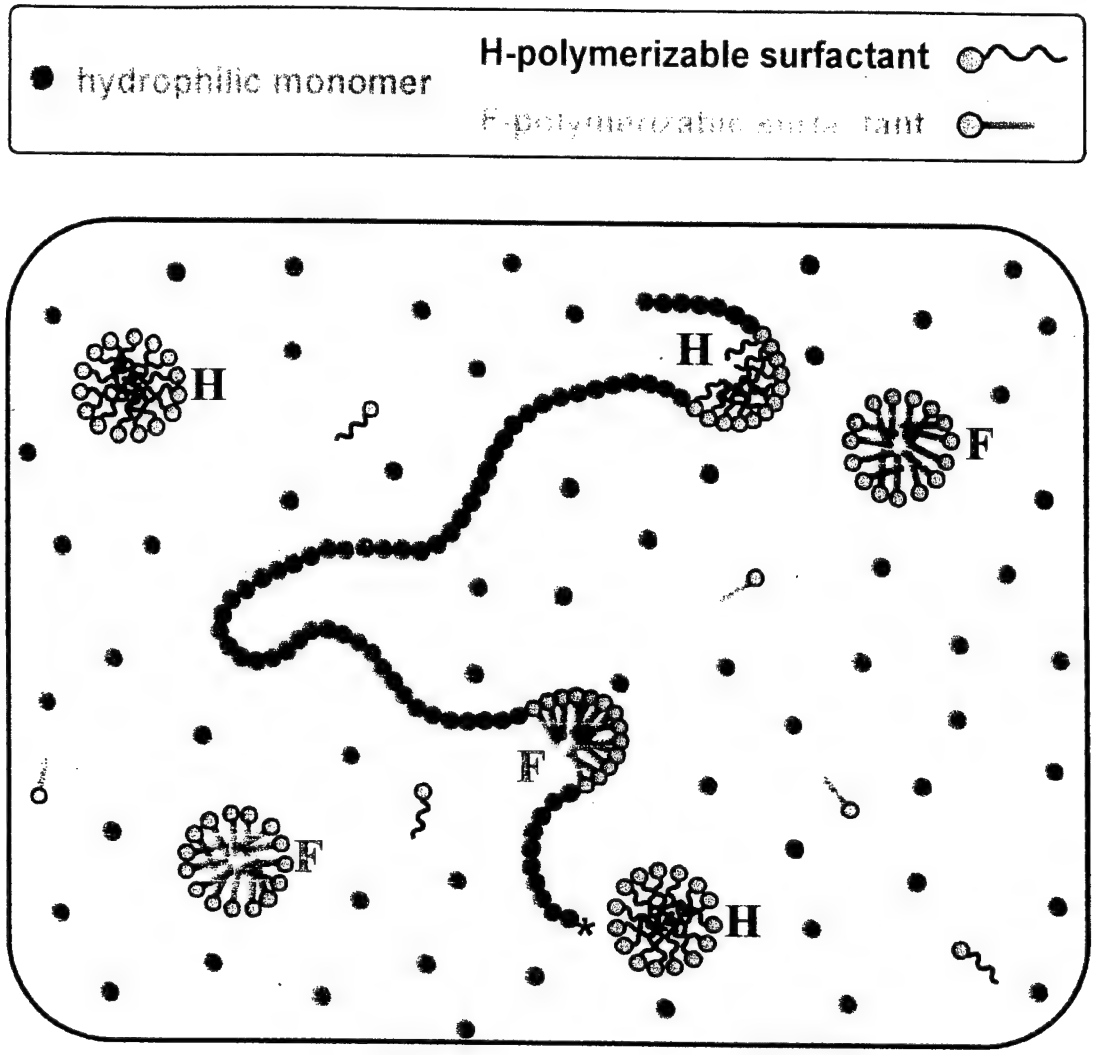
ong hydrophobic sequences with long alkyl side chains (C16)

⇩

polysoap like structure



Multicompartment Polymeric Micelles



water-soluble main monomer

+

hydrocarbon polymerizable surfactant

+

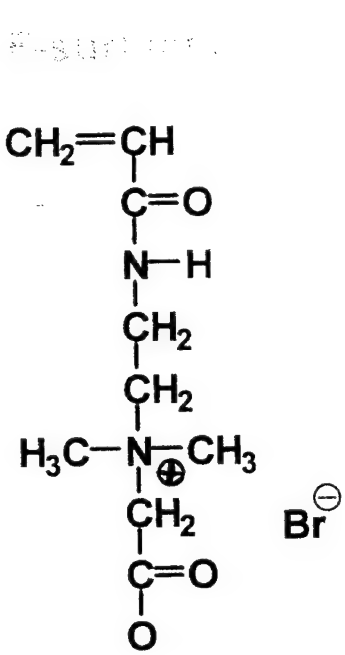
fluorocarbon polymerizable surfactant

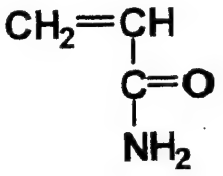
(demixed micelles)

⇩

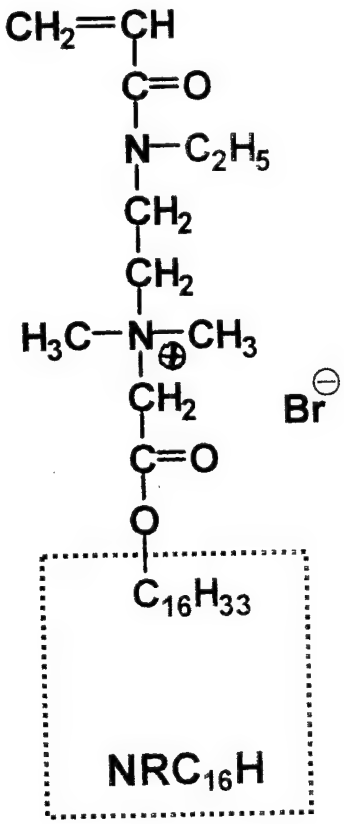
terpolymerization

INVESTIGATED SYSTEM





acrylamide (AM)



micelle formation

T_{Krafft} < 0°C

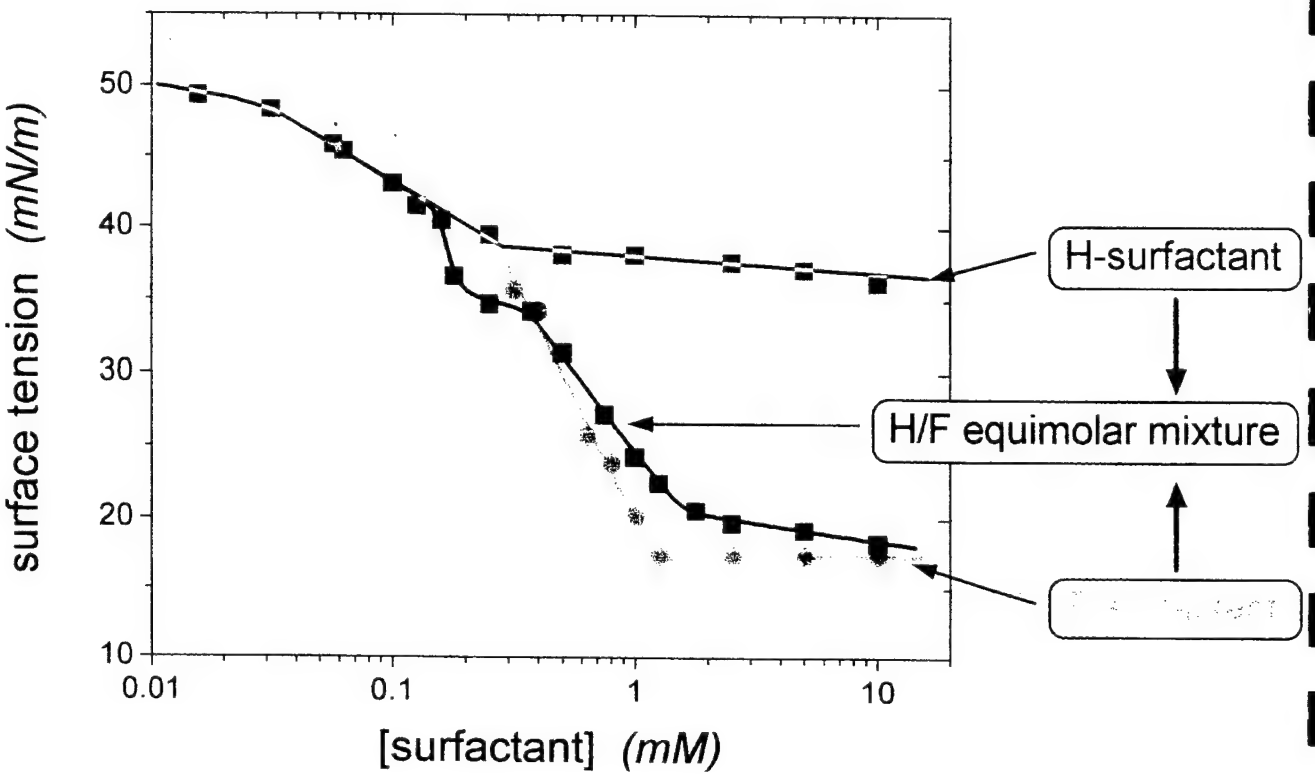
$cmc_{30°C}$ = 0.71 mM

T_{Krafft} = 31°C

$cmc_{32°C}$ = 0.27 mM

K. Stähler, J. Selb, F. Candau, *Langmuir*, 15, 7565 (1999)

Surface Tension Experiments



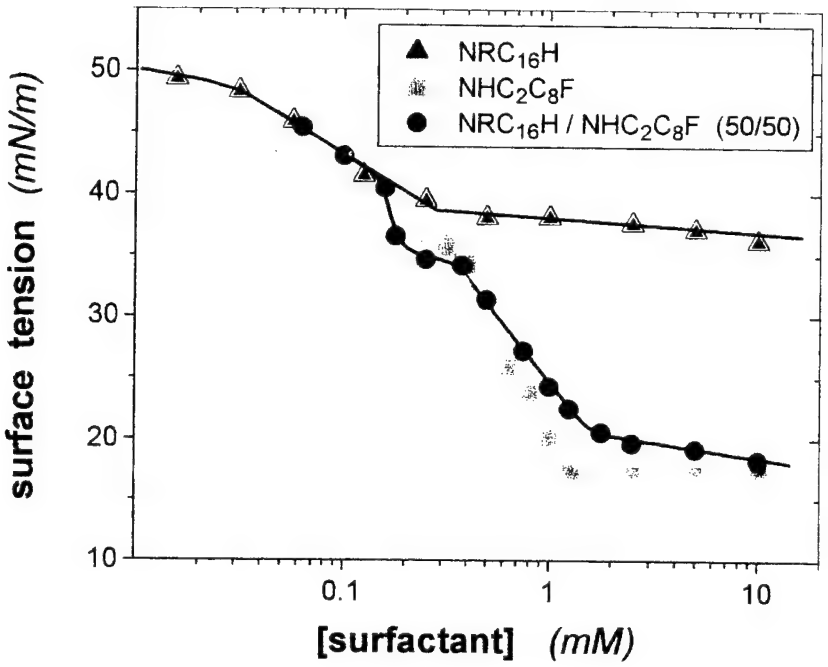
two cmc values

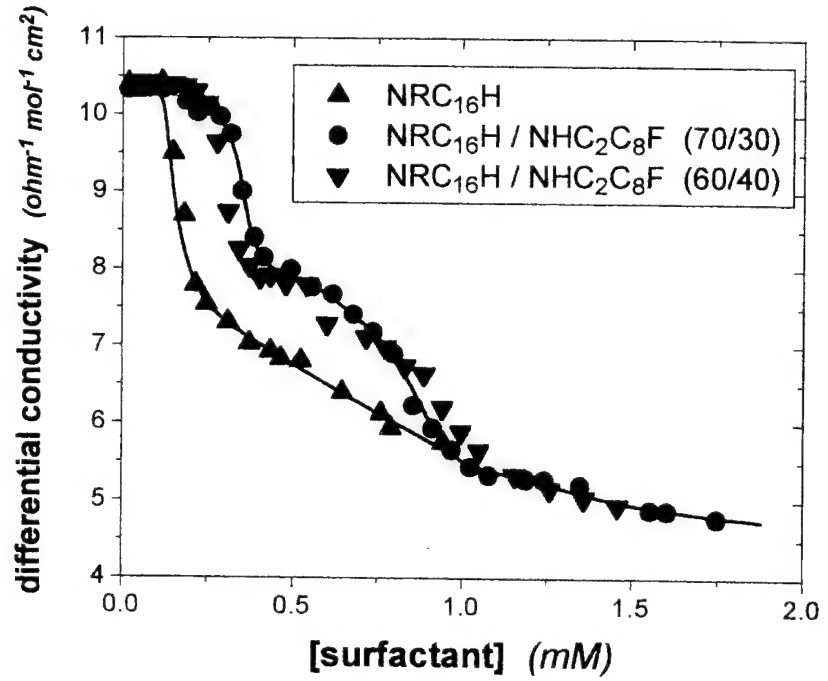
⇩

two kinds of micelles

Surfactant Mixed Micellization

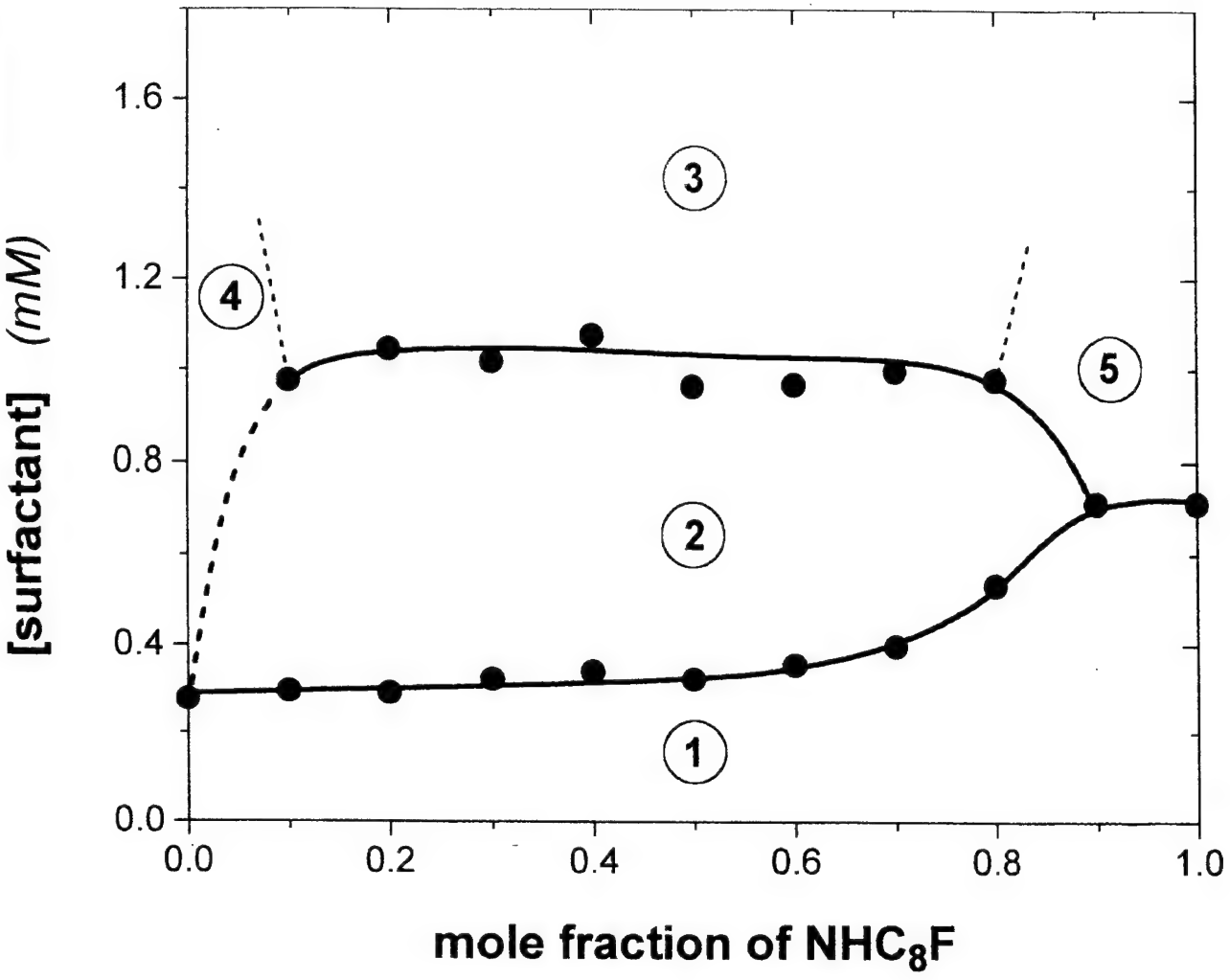
surface tension and conductivity studies





two cmc values ⇨ **two kinds of micelles**

Phase Diagram
NRC16H / NHC2C8F Mixed System



egion 1: ==> ***no micelles***

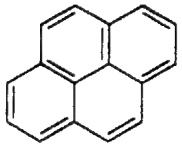
egion 2: ==> ***mixed micelles***

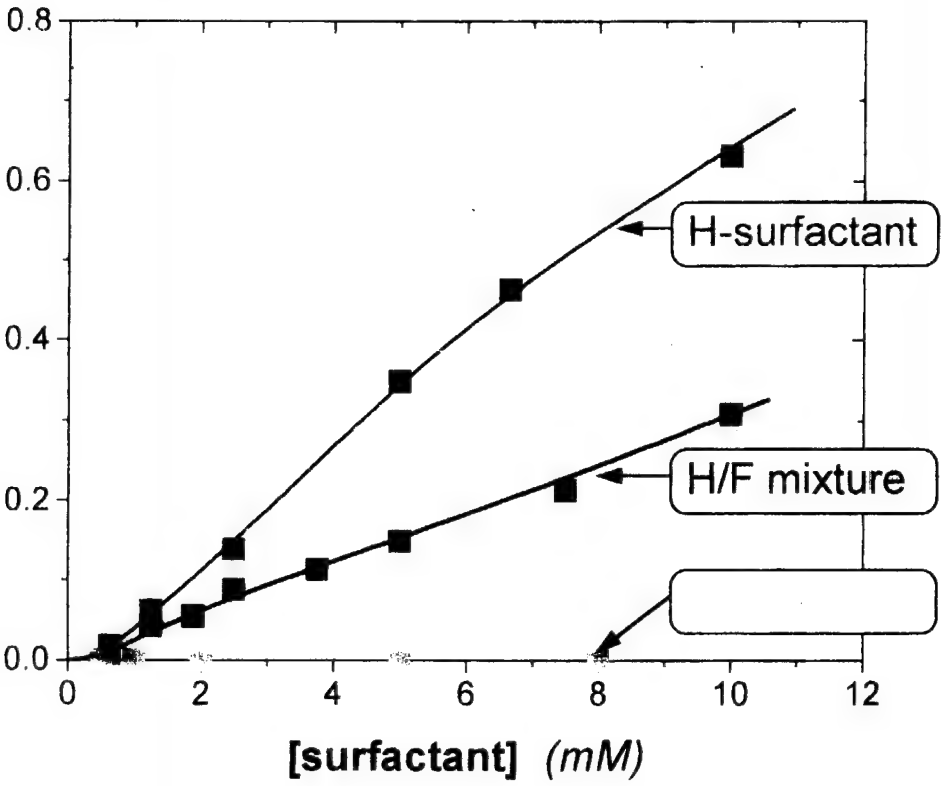
egion 3: ==> ***two types of micelles***

egions 4 and 5: ==> ***one micelle type***

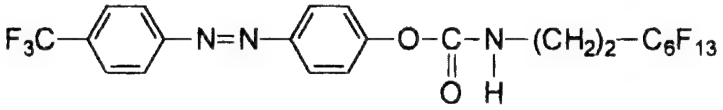
Solubilization of H- and F-dye in surfactant solutions

H-dye

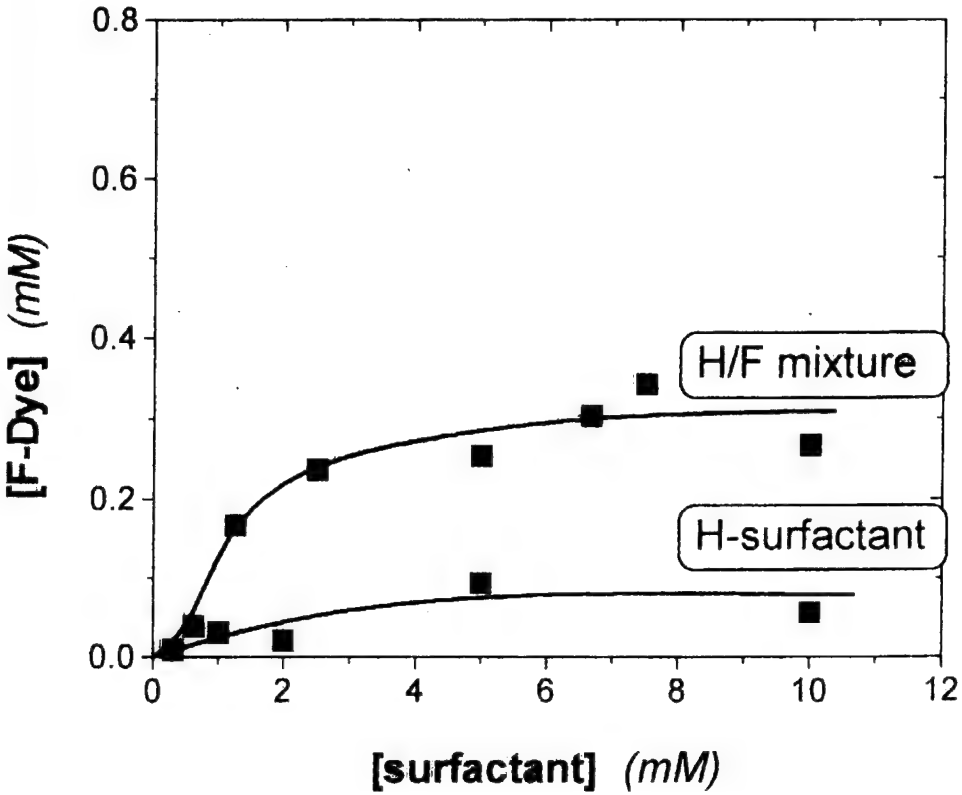




F-dye



(Pucci et al.)



Co- and Ter-polymerization in Aqueous Micellar Media

Monomers: (total : 2-3wt% in water)

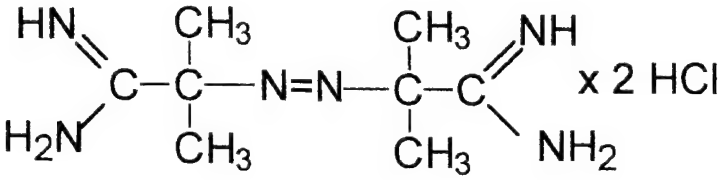
Acrylamide (98-99,5 mol/%)

H-surfactant (0,5-2mol%) and / or

F-surfactant (0,5-2mol%)

Initiation :

by UV- at ***32°C*** with the cationic ***V-50*** azo-initiator



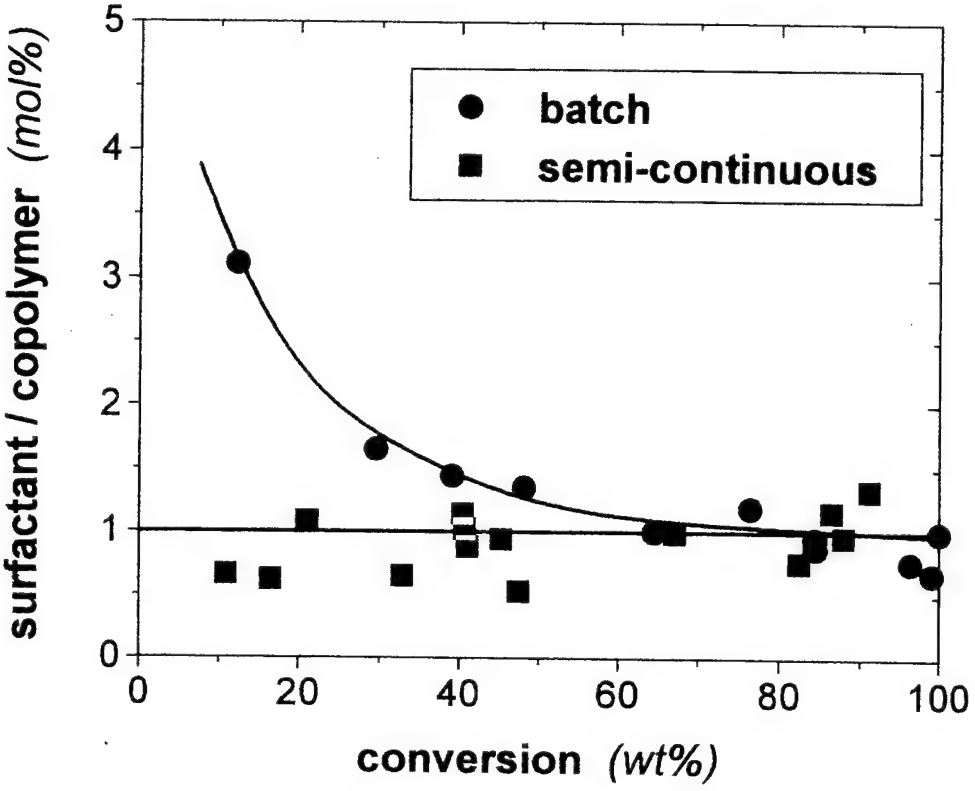
Process :

- ***batch*** polymerization
- ***semicontinuous*** polymerization :

  progressive addition of the micellar surfactant solution

H-surfactant / AM Copolymerization

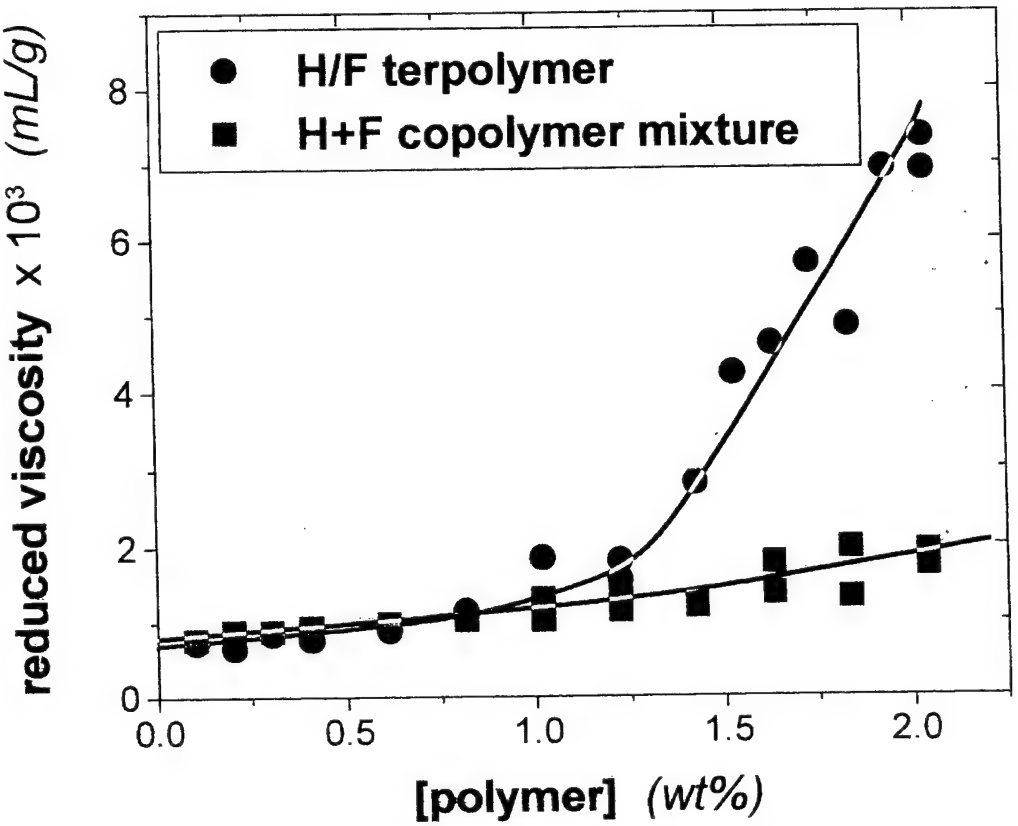
Kinetics of Surfactant Incorporation



semi-continuous process

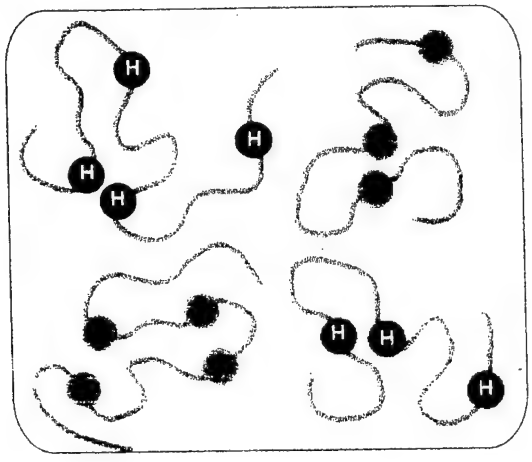
homogeneity in composition of the copolymer

Viscosity of the Aqueous Polysoap Solutions



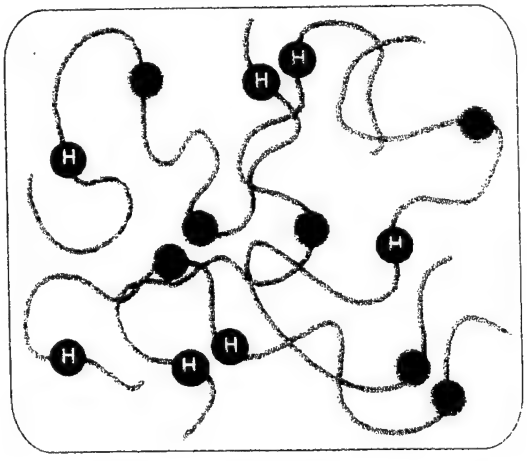
Hydrophobic Interactions

H/F Copolymer Mixture



microphase separation

H/F Terpolymer



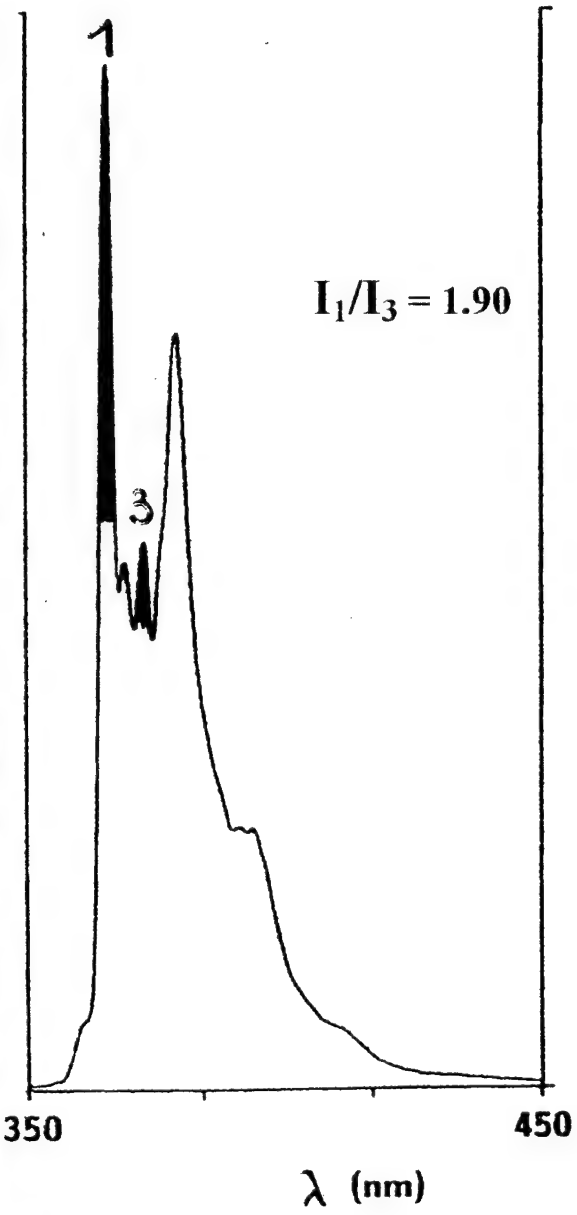
transient network

Fluorescence

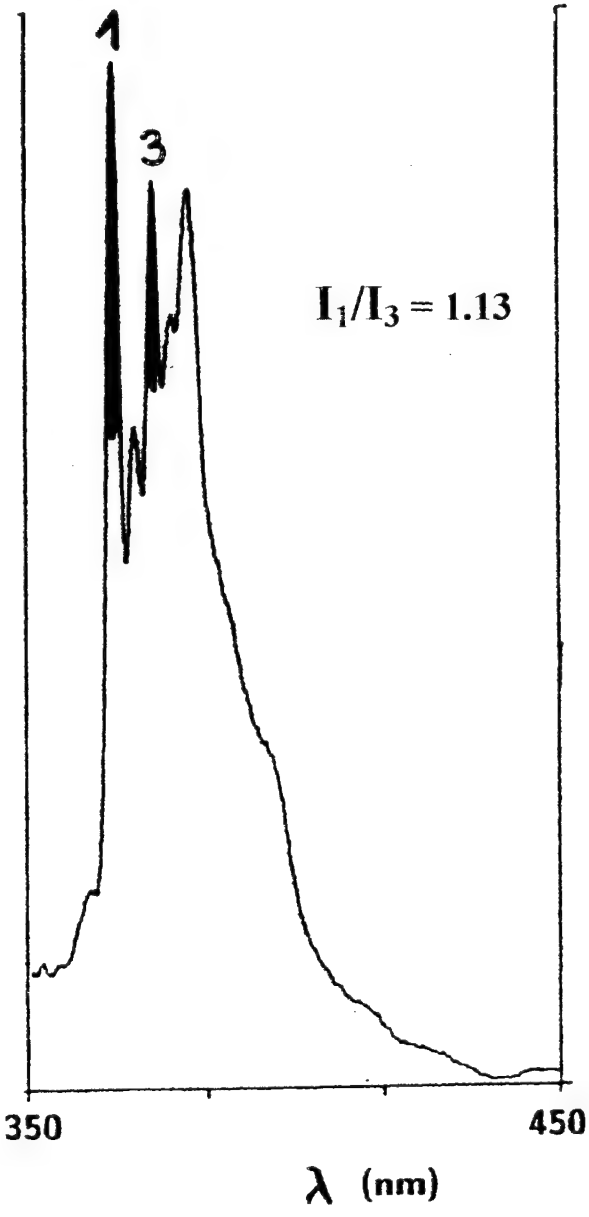
Pyrene emission spectra (I_1/I_3 ratio)

very sensitive to polarity of the microenvironment

/ water



/ toluene

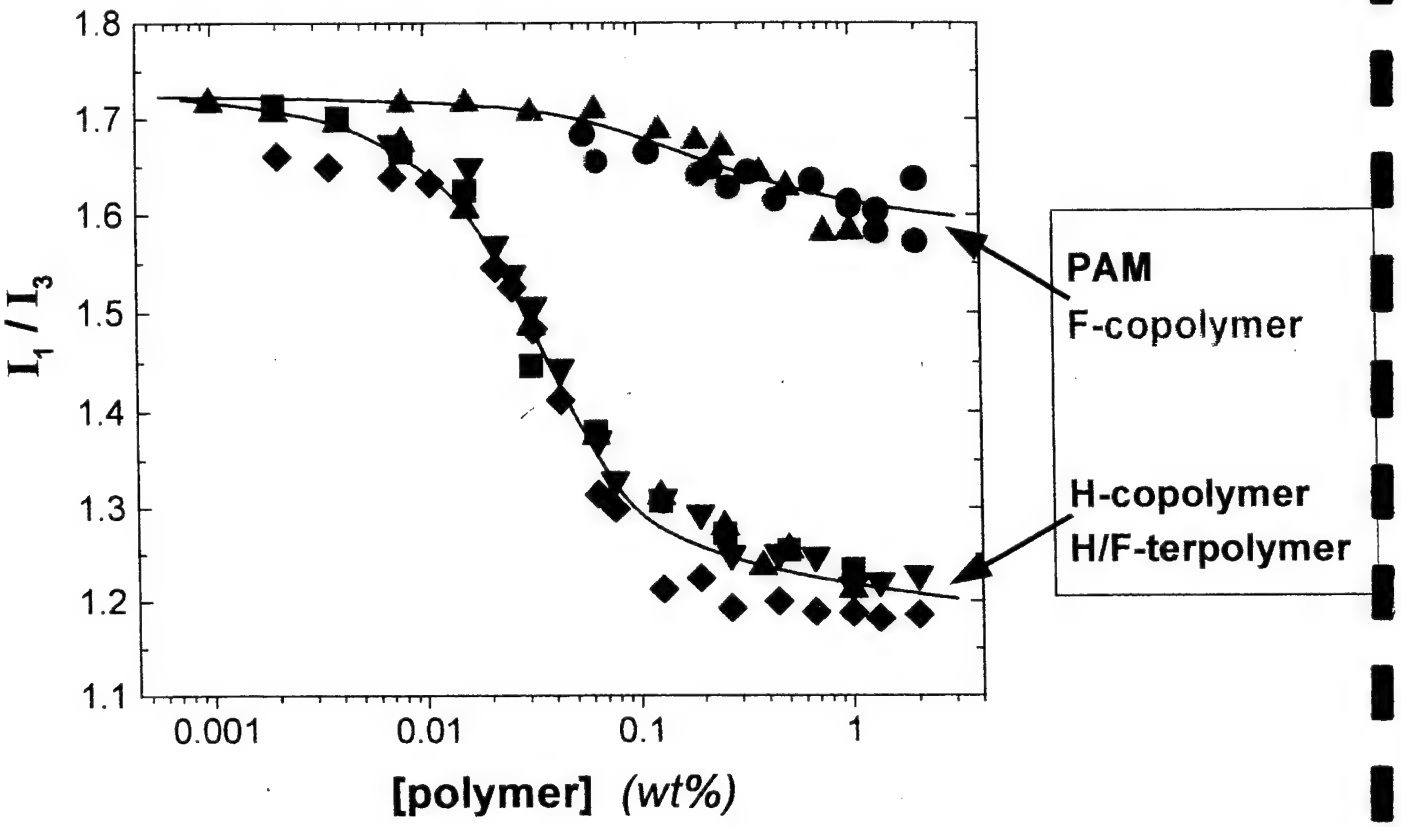


I_1/I_3 ↘ ⇔ hydrophobicity ↗

Fluorescence Probe Studies

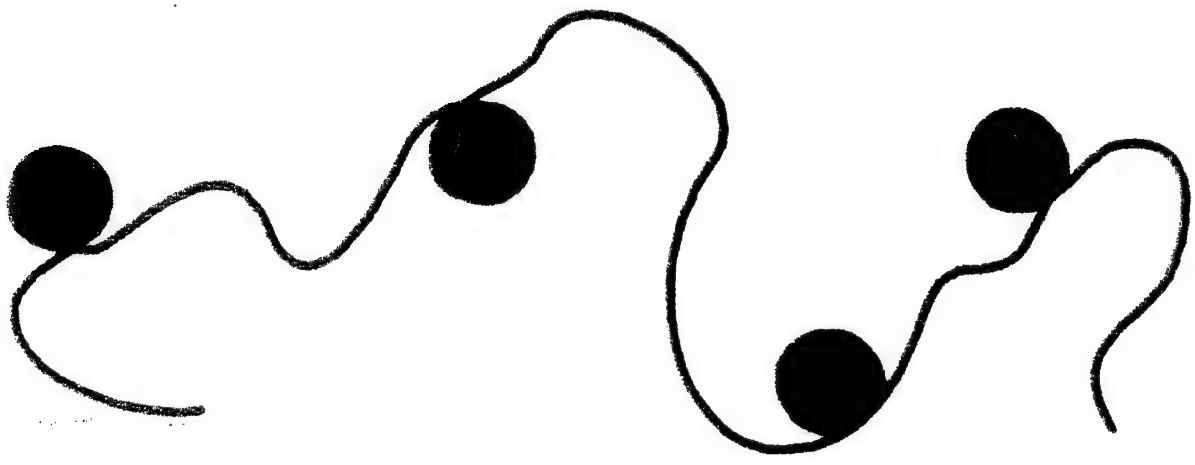
Pyrene emission spectra (I_1/I_3 ratio)

I_1/I_3 ↘ ⇔ hydrophobicity ↗

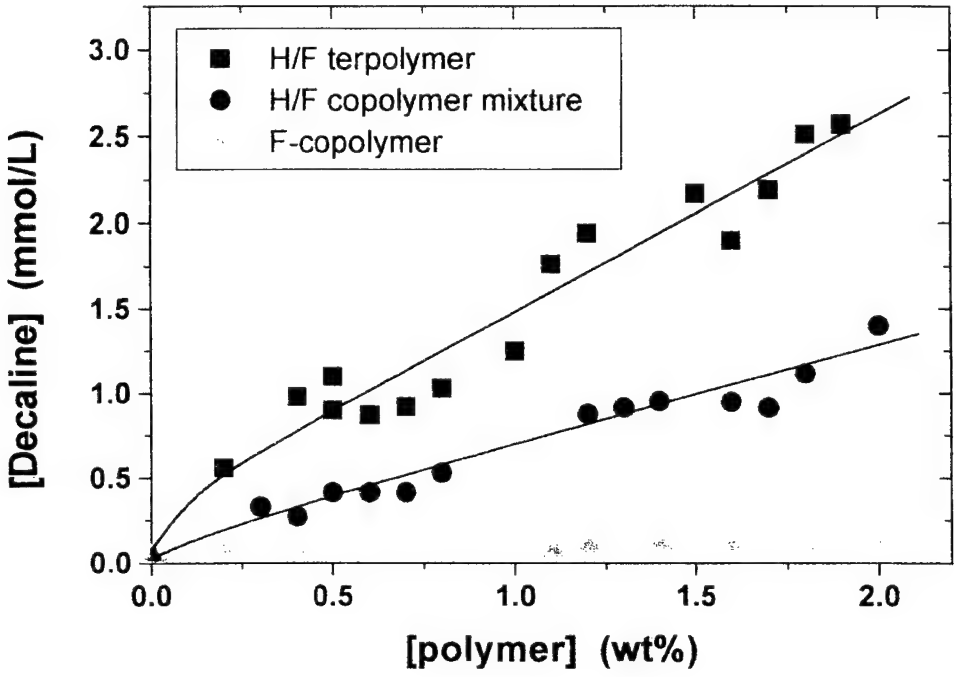


Multicompartment Polymeric Micelles

a string of polymer pearls



Solubilisation of Decaline in Polymer Solutions

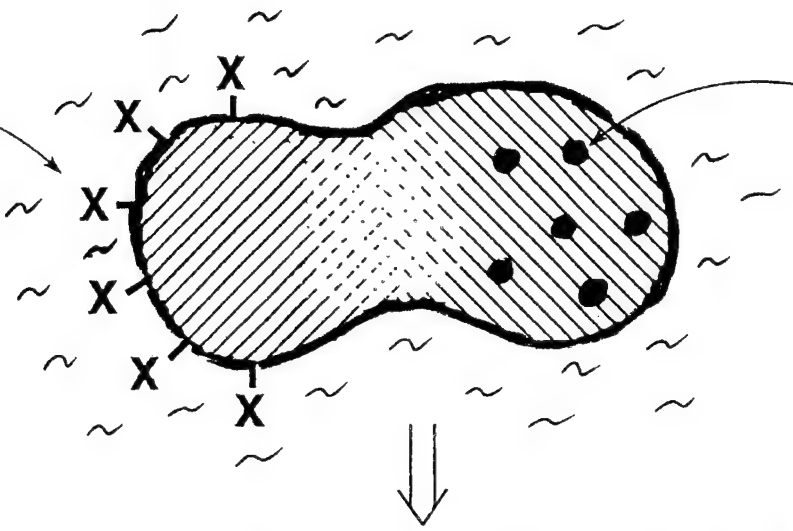


H/F Terpolymer: improved solubilisation capacity

H. Ringsdorf 16

MULTICOMPARTMENT MICELLAR AGGREGATES

Carriers in water with different Properties of the different Compartments :



Interaction with Surfaces

Solubilisation of guests ●

Application Possibilities ?

Agricultural Delivery	Biomedical Devices	Surface Variation	Organized aqueous Phases
- Herbicides	- Encapsulation	- Wetting	- Thickeners
- Fungicides	- Diagnostics	- Tribolic Systems	- Floculants
- Fertilizer	- Drug Delivery	- Biosensors	- Micelles

Université catholique de Louvain

Département de Chimie

A. Kotzev, A. Laschewsky, R. Rakotoaly

(1)

New Micellar Monomers and Polymers Bearing Perfluorocarbon Chains

I - interest in micellar polymers

II - synthesis of fluorocarbon surfactants

III - variation of polymer architecture:
homopolymers, statistical and block
copolymers with -(CH_2)- and -(CF_2)- chains

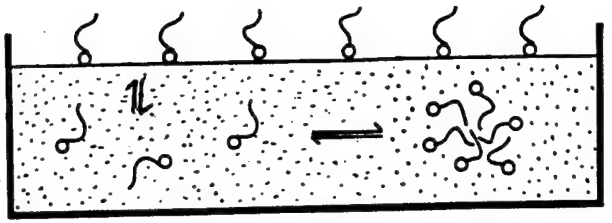
IV - multicompartment micelles

POLYSOAPS

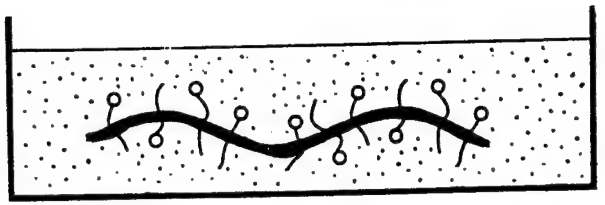
(Strauss et al. 1951)

Surfactants exhibit aggregation equilibrium

(2)



modified by polymerisation :

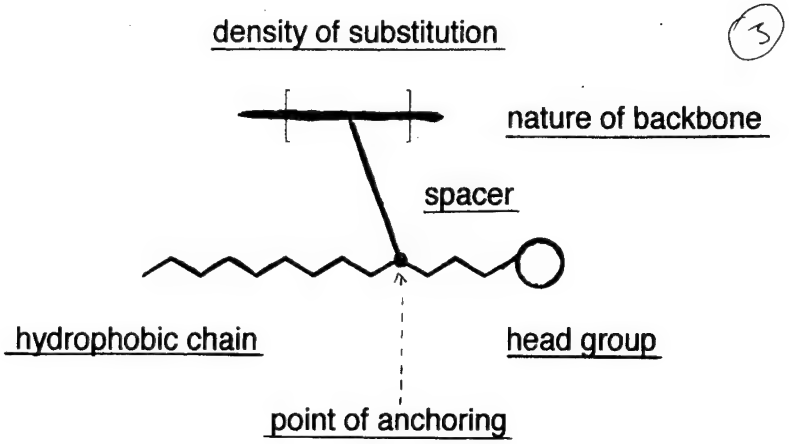


- different dynamics (e.g. no unimers)
- no critical concentration for aggregation

- surface activity ?
- solubilization ?
- emulsifying properties ?

- new superstructures ?

Molecular Parameters of Polymeric Soaps



⟹ highly variable due to superposition of parameters characteristic for amphiphiles and for polymers

Polymerizable Perfluorinated Surfactants

model: $CH_3-(CH_2)_n-N^+(CH_3)_2-R\ Cl^-$

⟹ $CF_3-(CF_2)_6-C(=O)-N$ (piperazinium, N^+ bearing CH_3 and CH_2-aryl, Cl^-)

guidelines for molecular design:

- avoid base sensitive $-CF_2-CH_2-$ group
- use stable linker groups (amide > ester)
- use tertiary amides (hydrophilic, no acidic -NH-)
- prefer 1:1 trans/cis conformers
- distribute polar fragments advantageously in amphiphile
- polymerizable moiety resistant to hydrolysis
- facile variation of polymerizable group possible

problem of cyclic head group:
high Krafft-temperature (± 65°C)

→ use one more flexible $-CH_2-$ link

→ or use open-chain analogue

Surface Activity of Reactive Fluorinated Surfactant

(6)

- strong reduction of surface tension at cmc
- cmc of 0.25 g/L = 3.5×10^{-4} mol/L compares well with model compound

cmc = 2.9×10^{-4} mol/L

Synthesis of Polymerizable Fluorocarbon Surfactants

attempted synthesis

observed pathway — - HCl, -HF

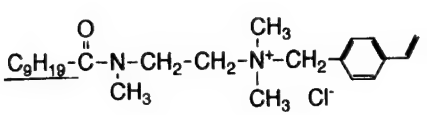
(mechanism is hypothetical)

(5)

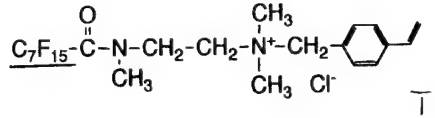
product obtained

Surface Activity of Reactive Fluorinated Surfactant

comparison of hydrocarbon and fluorocarbon analogues

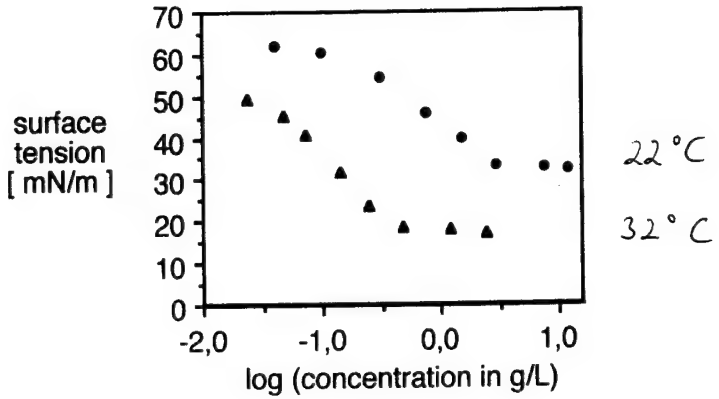


●



▲

$T_{Krafft} \approx 28°C$

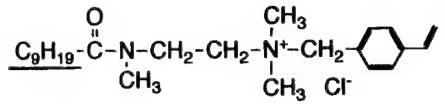


- fluorocarbon C_8-chain more hydrophobic than hydrocarbon C_{10}-chain
- surface tension more strongly reduced by fluorocarbon

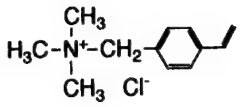
Synthesis of Fluorocarbon Polysoaps

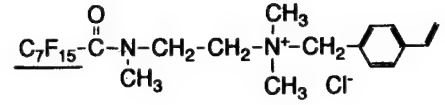
polysoaps of head-type geometry by copolymerization

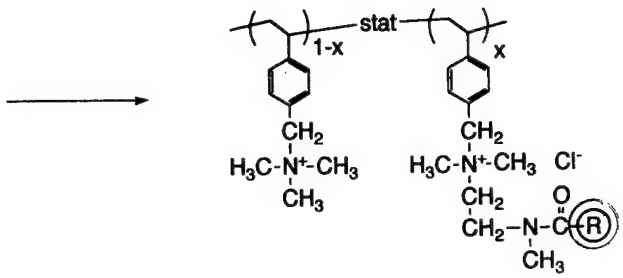
polymerizable surfactant "surfmer" + hydrophilic comonomer "spacer"



+





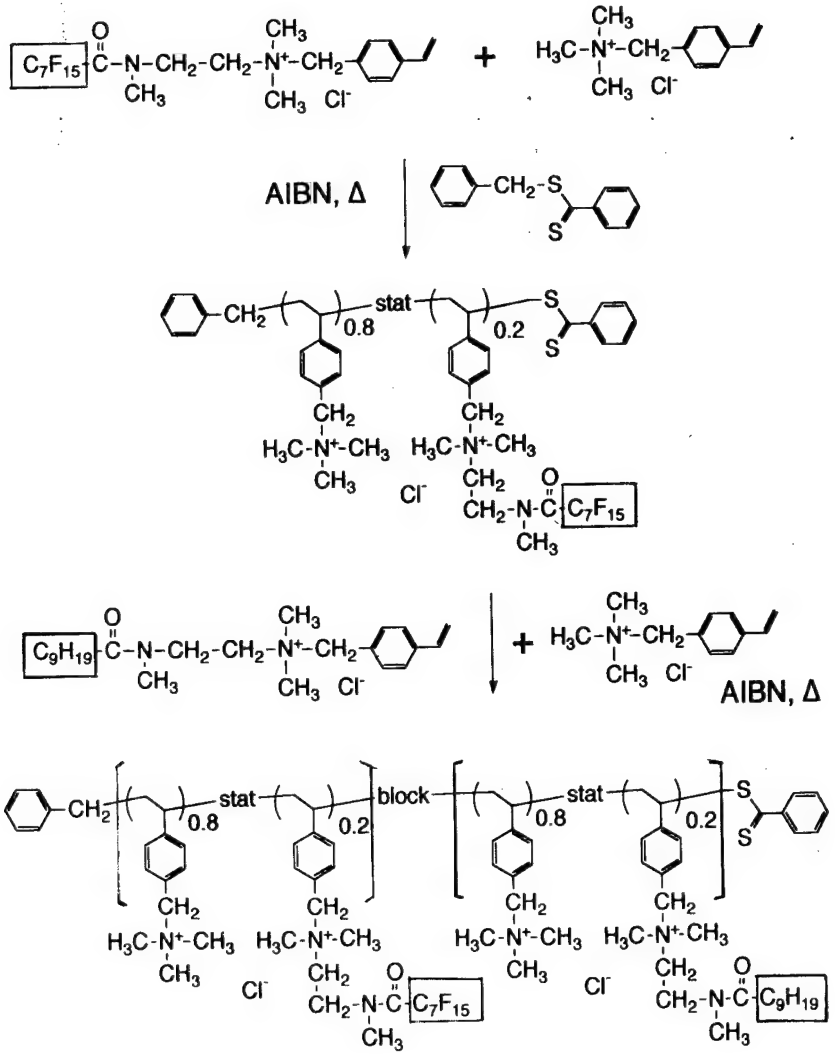


- hydrocarbon and fluorocarbon analogs
- no sensitive $-CF_2-CH_2-$ linkage
- hydrolysis resistant
- facile variation of hydrophobe content
- freely soluble in water up to about 25mol% of surfmer

Synthesis of Multicompartment Polysoaps

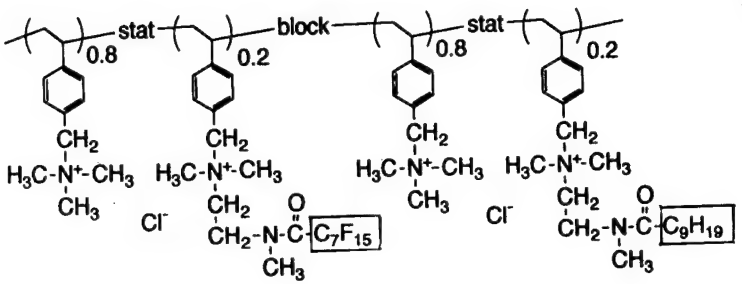
using controlled free radical polymerization: RAFT

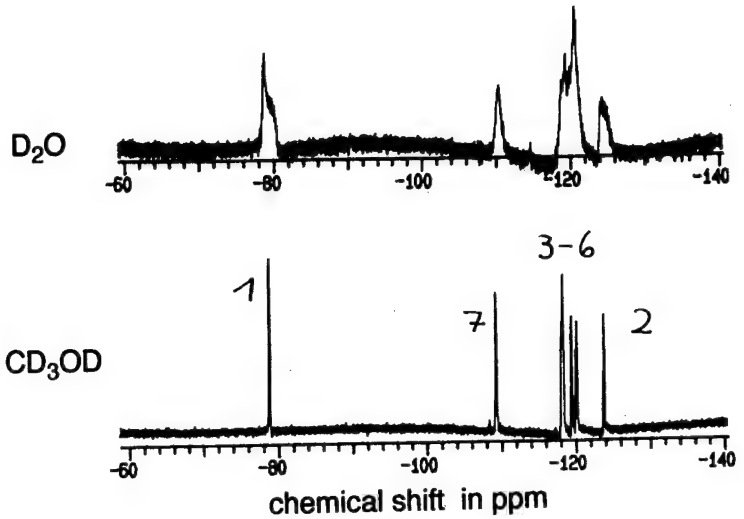
statistical copolymerization employing reversible chain-transfer



^{19}F-NMR-spectra of Block-Copolymer Soaps

effect of solvent





strong broadening of signals in water

→ hydrophobic aggregation

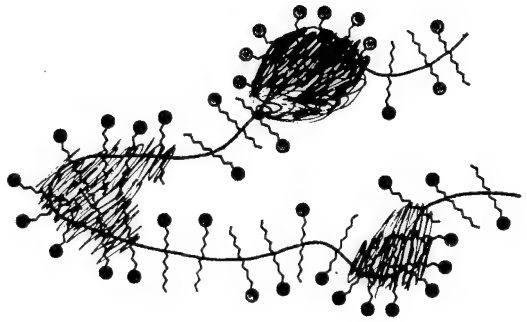
→ fluorocarbon chains little mobile

⇒ capacity for solubilization will be low for any compound

⇒ slow uptake/release kinetics

Strategies to Multicompartment Micelles

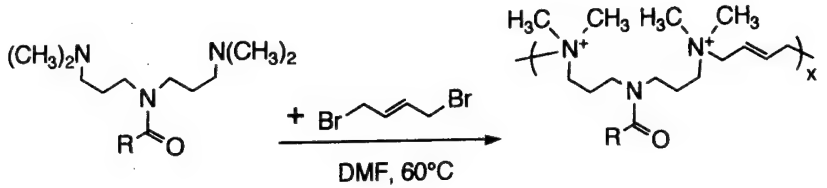
use of incompatible block copolymers



microphase separation induced by incompatibility of hydrocarbon and fluorocarbon chains ?

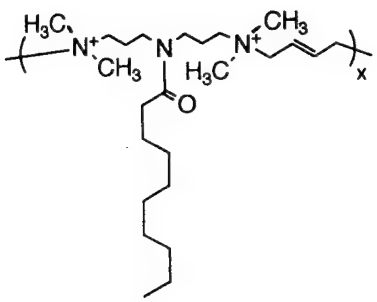
Ionenes Modified with Hydrophobic Chains

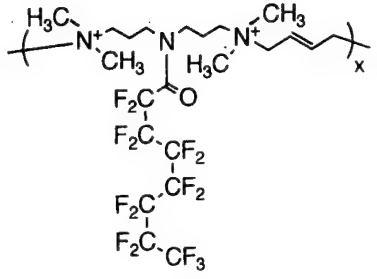
polysoaps by polycondensation (via Menschutkin reaction)



- high molar masses
- freely water-soluble
- hydrophilic, flexible main chain spacer
- adjustable structure:
  length of spacer is easy to vary,
  as is type of hydrophobic side chain

→ e.g. hydrocarbon and fluorocarbon analogs

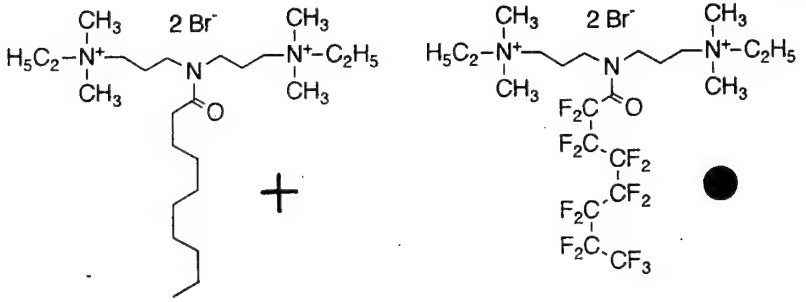


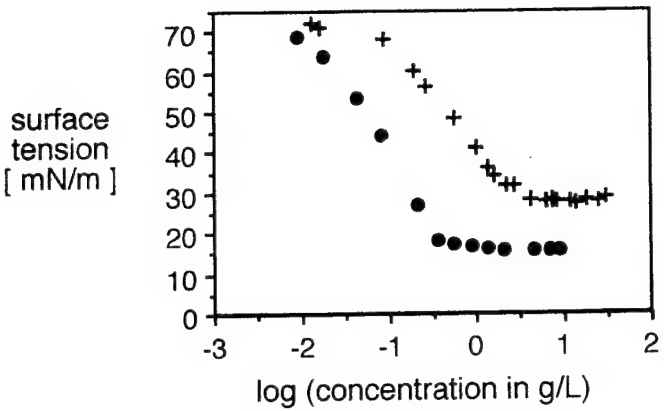


Micellar Properties of Two-headed Surfactants

comparison of hydrocarbon and fluorocarbon analogues

(13)



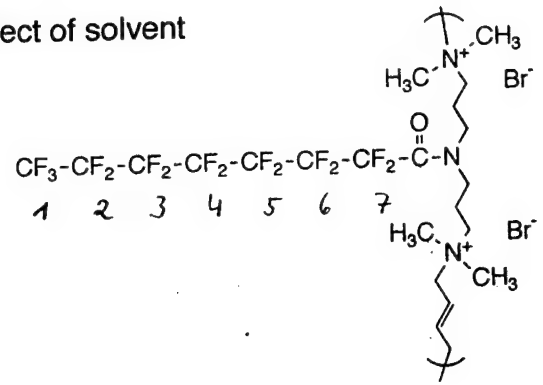


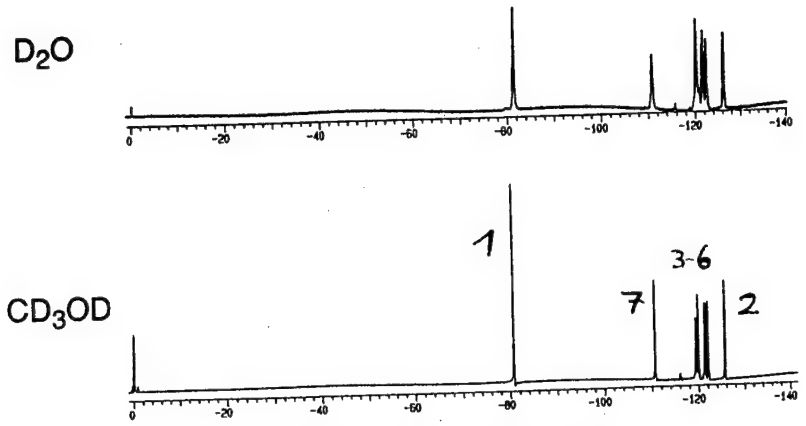
- fluorocarbon C_8-chain more hydrophobic than hydrocarbon C_{10}-chain
- surface tension strongly reduced by both surfactants

^{19}F-NMR-spectra of Fluorocarbon Polysoaps

effect of solvent

(14)





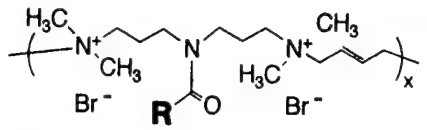
chemical shift in ppm

broadening of signals in water

→ hydrophobic aggregation

→ fluorocarbon chains rather mobile

Surface Activity of Amphiphilic Ionenes

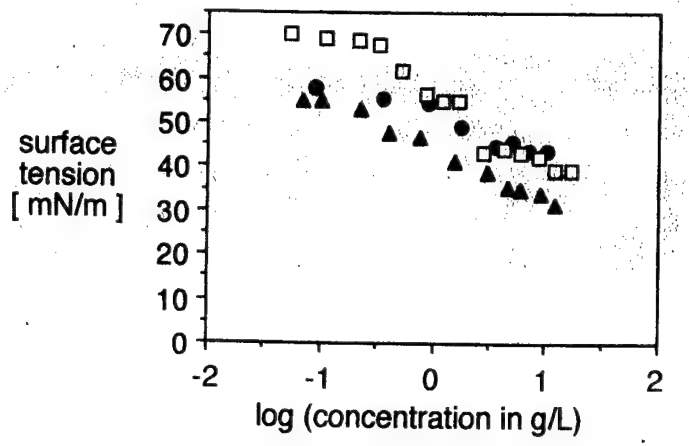


comparison of hydrocarbon and fluorocarbon analogues,

R: = $-C_9H_{19}$ (homopolymer CH) ●

R: = $-C_7F_{15}$ (homopolymer CF) ▲

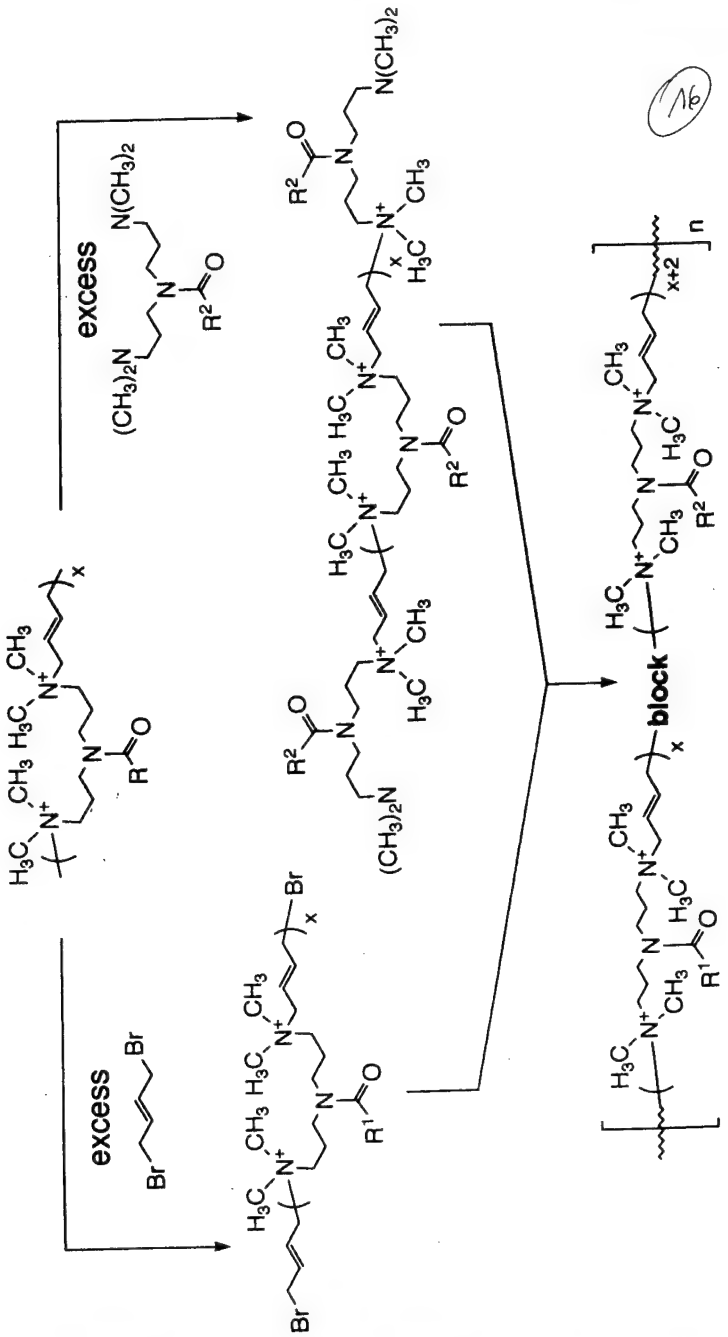
R: = statistical 1:1 copolymer □



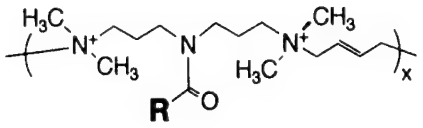
- all polymers surface active
- fluorocarbon analogue is relatively the most active
- no indication for a critical micelle concentration CMC

Synthesis of Ionene Type Block Copolymers

by stepwise, irreversible polycondensation



Reduced Viscosity of Hydrophized Ionenes in Water



(17)

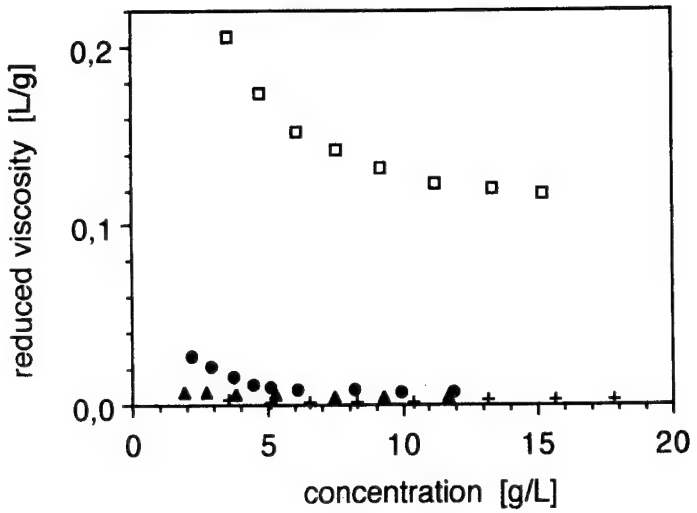
comparison of hydrocarbon and fluorocarbon analogues

R: = $-C_9H_{19}$ (homopolymer CH) ●

R: = $-C_7F_{15}$ (homopolymer CF) ▲

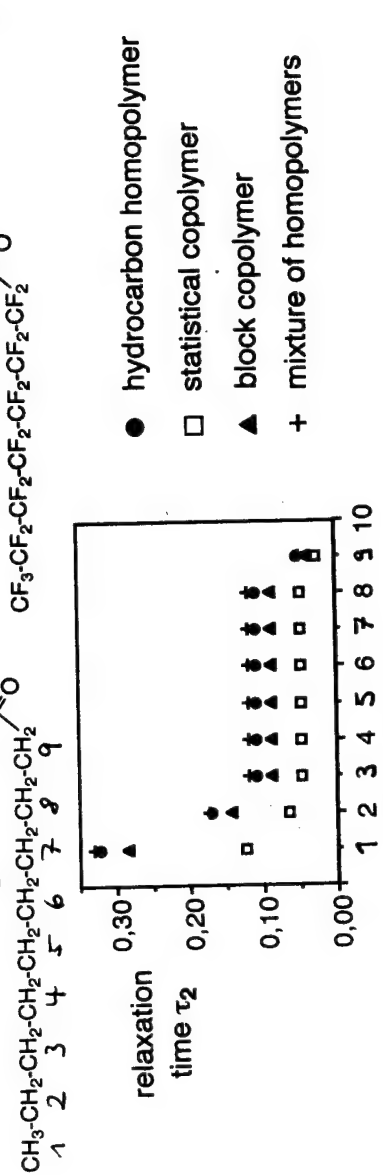
R: = statistical copolymer □

R: = block copolymer +



- polyelectrolyte behaviour
- reduced viscosities low → hydrophobic aggregation
- statistical copolymer gives highest viscosities by far

^{1}H-NMR Studies of Hydrophobized Ionene Block Copolymers



(19)

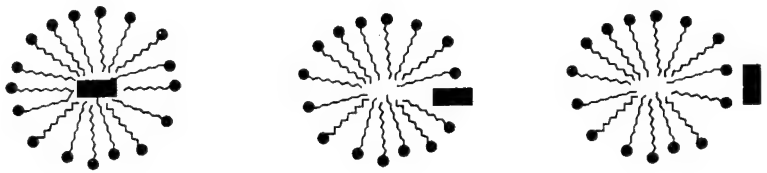
- profiles of τ_1 and τ_2 values indicate decreasing order within hydrocarbon chains
- block copolymer behaves very similar to homopolymer
  → suggests microphase separation

A. Kotzev
P. Adriaensens

Solubilization by Micelles

key property of surfactant aggregates

solubilizate ■

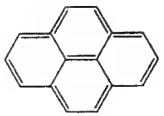


in core | at surface | on surface

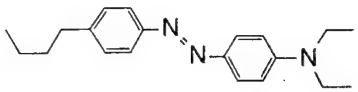
solubilization site depends on molecular structure of solubilizate

- polarity - form - size

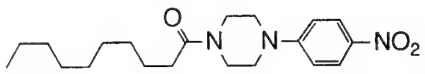
hydrophobic dyes for solubilization studies



purely aromatic



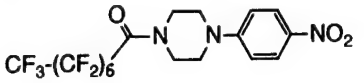
bulky and polar



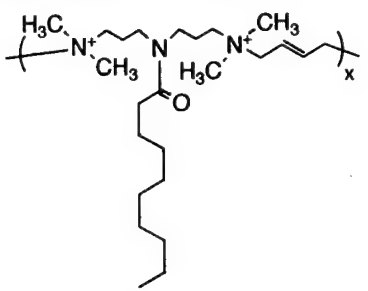
weak amphiphile

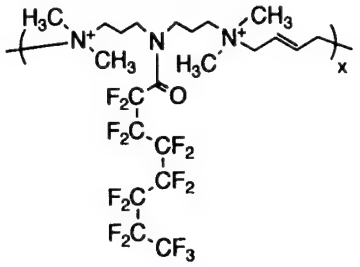
Solubilization by Hydrophobized Ionenes

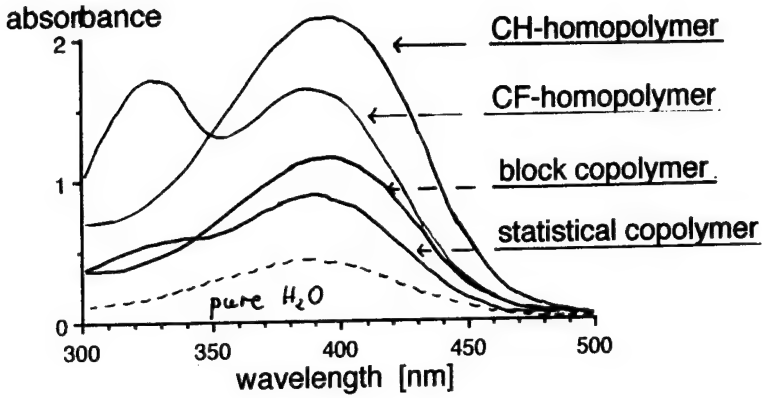
dye studied



using different polymer architectures derived from parent ionenes



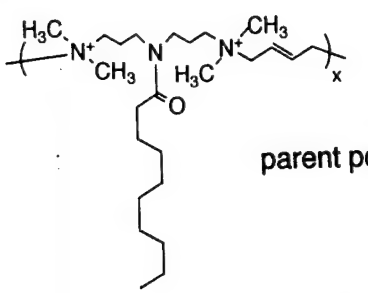


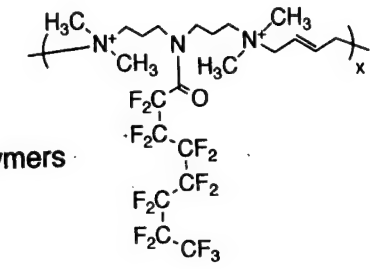


- both hydrocarbon and fluorocarbon analogs solubilize dye
- fluorocarbon polysoap induces dye aggregation
- block copolymer behaves like hydrocarbon homopolymer
- statistical copolymer shows intermediate behaviour

Solubilization by Hydrophobized Ionenes

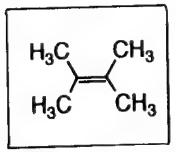
in dependence on their polymer architecture, as studied by NMR

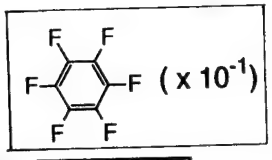




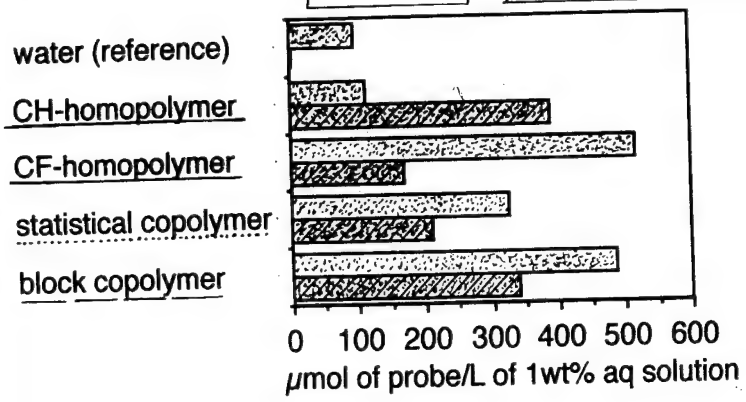
parent polymers

probes used





(x 10^{-1})



- both hydrocarbon and fluorocarbon analogs solubilize probes
- fluorocarbon probe best solubilized by CF-homopolymer and by block copolymer
- hydrocarbon probe best solubilized by CH-homopolymer and by block copolymer

Summary

- several synthetic strategies are feasible to obtain mixed CH/CF-block copolymers
- fluorocarbon ionenes are particularly interesting
- polymeric multicompartment micelles can be realized
- properties of such new superstructures ???

Acknowledgements

IUAP/PAI 4/11 Belgian State

FLUORINATED AND SEMIFLUORINATED COMPOUNDS : SYNTHESIS, GENERALIZATION OF THE AMPHILILIC CONCEPT AND APPLICATIONS.

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One of the objective of our laboratory being the development of novel mixed fluorinated and hydrogenated molecule we prepared new fluorinated Wittig reagents, very useful for the synthesis, in formamide, of mixed molecules. Then we prepared olefins from which we studied :

* the cycloaddition reaction with cyclopentadiene, and the aggregation properties of obtained substitued norbornenes (primitive surfactants),
* the amidation reaction in formamide microemulsions ;
* their ability to provide new formulations for blood substitutes or their applications in vitreous surgery.

We also prepared new surfactants having polar heads from lactose and glucose derivatives. An interesting phenomenon of gelification in formamide was observed with surfactants synthesized from gluconolactone.

Perfluorinated or semifluorinated hydrocarbons have special properties owing to the characteristics of the fluorine atom : particularly the hydrophobicity of the fluorinated chains and their segregation behaviour towards perhydrogenated compounds. We explored these properties in order to develop new syntheses and new applications in biology or medecine. Our last results in this field was the preparation of a new mixed double chain catanionic derivative. This compound forms spontaneous veiscles useful to encapsulate AZT after sonication. The stability and morphology of these vesicles have been studied by dynamic light scattering and TEM freeze fracture replica

1 Semifluorinated olefins : synthesis and aggregation properties

2 Mixed oils and biological applications

3 Reactivity of mixed oils : new surfactants preparations

4 Fluoroalkylglycolipids

- long fluoroalkyl chain glycolipids
- catanioinic glycolipids

I – Semifluorinated olefins : synthesis and aggregation properties

1) Diels-Alder reaction

In order to investigate new synthesis of mixed derivatives, we attempted the preparation of bicyclo [2.2.1] hept-2-enes, mono and disabstituted with long perfluorinated groups : such compounds were also interesting monomers for obtaining mixed polymers.

These derivatives were synthesized by a Diels-Alder reaction between cyclopentadiene and olefins with perfluorinated chains $R_FCH=CH_2$ and R_F-CH=CH-R_F (scheme 1).

The ^{19}F spectra of these derivatives carried out in $CDCl_3$ at the probe temperature (23°) differed considerably for different chain lengths R_F. We postulated that these differences could be attributed to intermolecular associations.

Such associations were probably limited to segregation processes between the fluorinated and hydrogenated groups. This is a well known phenomenon in mixtures of perfluorinated and perhydrogenated compounds (1).

This process leads to the association of the bicyclic derivatives which behave as amphiphilic molecules with a large hydrogenated head (bicyclomoiety) and a long perfluorinated tail. Associations of this type can lead to the formation of micelles (Fig. 1).

This hypothesis was confirmed by studying :

1) the effect of temperature : the micellar structures being sensitive to temperature. We carried out an investigation of the ^{19}F NMR spectrum of R_F monosubstituted norbornenes in $CDCl_3$ at different temperatures and observed the destruction of the aggregate with liberation of free molecules when the solution was enough heated.
2) the effect of concentration. With $R_F=C_4F_9$ in the concentration range studied (0.4 to 2.10^{-7}mol.l^{-1} in $CDCl_3$) the association process appeared to persist.

In the same time. M.P. Turberg and J.E. Brady showed that semifluorinated hydrocarbons

CF_3- $(CF_2)_7$-$(CH_2)_{11}CH_3$ and CF_3-$(CF_2)_7$-$(CH_2)_{15}$-CH_3

form reverse micelles in perfluorotributylamine and perfluorooctane respectively (2). They gave semifluorinated hydrocarbons the name of "**primitive surfactants**".

Their work and our shown that ;

- the aggregation phenomenon in solution is general,
- the amphiphilic behavior only necessitates complementary parts in the molecule : one soluble in the solvent and the other no.

1 Semifluorinated olefins : synthesis and aggregation properties

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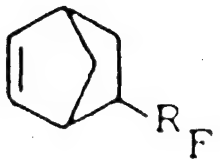
4 Fluoroalkylglycolipids

- long fluoroalkyl chain glycolipids
- catanioinic glycolipids

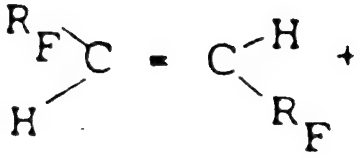
1) $R_F\text{-}CH{=}CH_2$ +  $\xrightarrow[72\ h]{170\,^\circ C}$ 

20% exo

80% endo

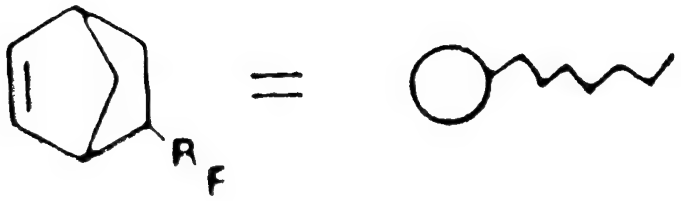
$R_F = C_4F_9,\ C_6F_{13},\ C_8F_{17},\ C_{10}F_{21}$

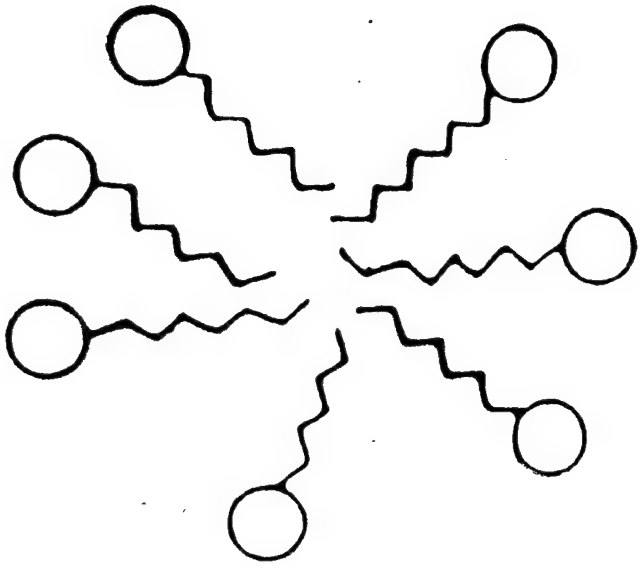
2)

 +  $\xrightarrow[72\ h]{170\,^\circ C}$ 

$R_F = C_4F_9,\ C_6F_{13},\ C_8F_{17}$

Schema 1


R F



More recently, P.D.I. Fletcher and al (3) have studied the aggregation of semifluorinated alkanes (SFAs) in binary and ternary mixtures with hydrocarbon and fluorocarbon solvents. They showed that SFAs aggregate weakly in both hydrocarbon and fluorocarbon solvents.

2) Wittig reagents (scheme II and Tables I-III)

Taking advantage of the properties of formamide we prepared by Phase Transfer Catalysis, alkenes from aldehydes and perfluorinated Wittig reagents.

This, last reagents, insoluble in water are very useful for the synthesis of mixed molecules and presented aggregation properties in solution in formamide.

$$(C_6H_5)_3P + R_F(CH_2)_2I \xrightarrow{95°C,\ sans\ solvant} (C_6H_5)_3P^+(CH_2)_2R_F,I^-$$

$$(C_6H_5)_3P^+\text{-}C_2H_2\text{-}R_F,I^- + R_HCHO \xrightarrow{Wittig} R_FCH_2CH{=}CHR_H + (C_6H_5)_3P{=}O$$

Composé	$(C_6H_5)_3P^+ CH_2CH_2R_F, I^-$	Rendement (%)
1	$R_F = C_4F_9$	95
2	$R_F = C_6F_{13}$	94
3	$R_F = C_8F_{17}$	84
4	$R_F = C_{10}F_{21}$	90

Sels de phosphonium synthétisés

Composé	$R_FCH_2CH{=}CHR_H$	Rendement (%)
5	$C_4F_9CH_2CH{=}CHC_{11}H_{23}$	58
6	$C_6F_{13}CH_2CH{=}CHC_6H_5$	80
7	$C_8F_{17}CH_2CH{=}CHC_4H_9$	60
8	$C_8F_{17}CH_2CH{=}CHCH_2CH(CH_3)_2$	74
9	$C_{10}F_{21}CH_2CH{=}CHC_5H_{11}$	28

Oléfines mixtes synthétisées

N°	Composé fluoré	Densité	Tension superficielle (mN/m , 37°C)	Indice de réfraction (25°C)
7	$C_8F_{17}CH_2CH{=}CHC_4H_9$	1,45	19	1,342
8	$C_8F_{17}CH_2CH{=}CHCH_2CH(CH_3)_2$	1,5	19	1,338
	PFD	1,9	18	1,314

Quelques propriétés physiques des oléfines 7, 8

II – Semifluorinated olefins : Biological applications

1) Oxygen carriers : microemulsions with semifluorinated mixed oils.

Olefins particularly :

$$C_8 F_{17} CH_2\text{-}CH{=}CH\text{-}C_4H_9$$

are good oxygen solvents : it dissolves oxygen to as great an extent than F. decalin (Table IV).

With this oil we have been able to produce microemulsions (4).

As we know, perfluorocarbons are good oxygen carriers in articificial blood. In order to have injectable "blood substitutes", microemulsions are particularly attractive. However fluorocarbons are highly hydrophobic and lipophobic molecules due to segregation between fluorinated and hydrogenated chains.

Two strategies can be used :

1st The development of biocompatible fluorinated surfactants to microemulsify perfluorinated oils. In accordance with this strategy, new synthesis of non ionic fluorinated surfactants has been tried

2d The adaptation of the oil to a biocompatible surfactant.

We optimized an aqueous system with a biocompatible surfactant Montanox 80 used in the formulation of vaccines by the Institut Pasteur.

This diagram was realized at 37°C (body temperature) (Fig. 2).

The microemulsions are of the oil in water type which are well suited for use as blood substitutes.

Apart from microemulsion D, the others dissolved oxygen to a greater extent than Fluosol DA (Table V).

It should be noted that the theoretical values of oxygen solubility are much less than the measured values in microemulsions C, D, E which have a true micellar structure.

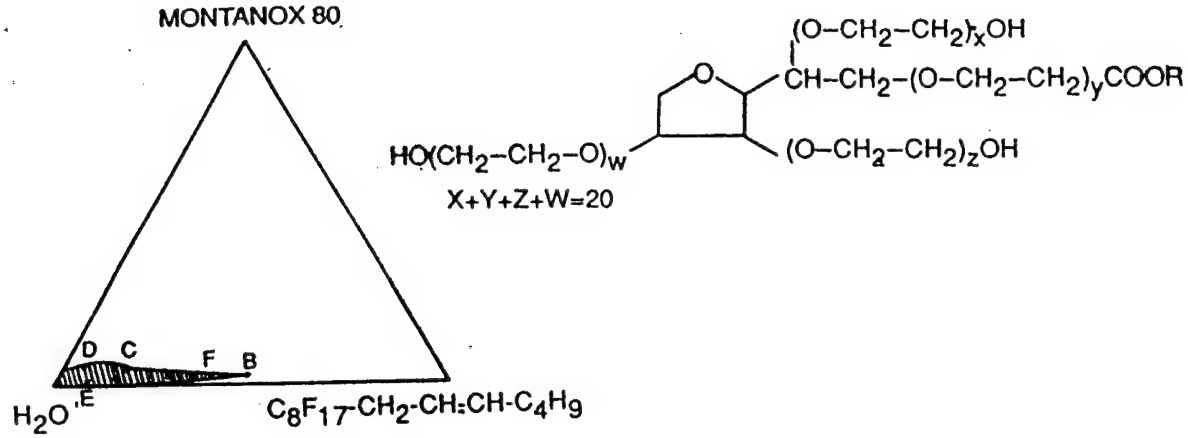
The excess of solubility was in fact 500 % indicating that the structure of the microemulsions increases their capacity to take up oxygen.

The toxicity of the microemulsions was tested after intraperitoneal injection in rats. and in mice after intravenous administration : the microemulsions appeared to be well tolerated (5). These results show promise for the development of oxygen transporting compounds.

The development of blood substitutes being very difficult, we proposed another application.

Composition of microemulsions (% weight)						O_2 absorption(ml/100ml)	
	Mx80	oil	H_2O	η(cp)	r(Å)	Measured	Calculated
B	2.6	48.7	48.7	70.0	-	23	17.0
C	5.5	16.6	77.8	1.1	64	32	5.4
D	7.15	7.15	85.7	1.1	36	9	2.3
E	1.3	9.1	89.6	0.9	43	21	2.8

Table IV



Composition of microemulsions (% weight)						O_2 absorption(ml/100ml)	
	Mx80	oil	H_20	η(cp)	r(Å)	Measured	Calculated
B	2.6	48.7	48.7	70.0	-	23	17.0
C	5.5	16.6	77.8	1.1	64	32	5.4
D	7.15	7.15	85.7	1.1	36	9	2.3
E	1.3	9.1	89.6	0.9	43	21	2.8

Table V Characteristics of microemulsions B, C, D and E.

Montanox 80 is a non-ionic surfactant manufactured by Seppic with an HLB of 14. It has a very low toxicity (oral LD50 > 16 ml/kg) and is used in the formulation of vaccines by the Institut Pasteur. It has the following formula :

2) Applications of mixed oils in vitreous surgery

The use of perfluorocarbon liquids has facilitated the surgical management of complicated retinal damages (Fig.3) However **retinal damages** occurs when some of such products are used as **long-term** vitreous replacement.

Mechamical alteration due to pressure and chemical impureties have been suggested to explain this behavior.

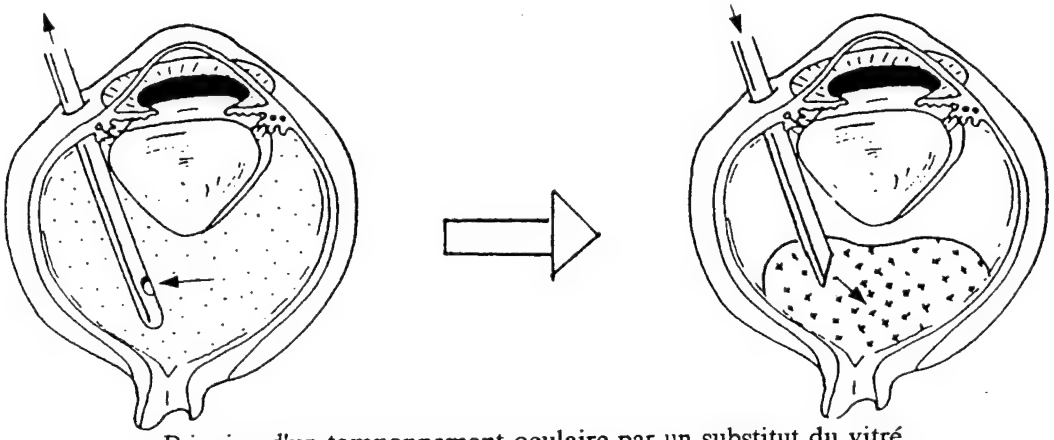
With mixed oils it is possible to modulate the density of liquids by changing the relative lenghts of the perfluorinated and perhydrogenated parts.

This last property is very useful for surgeons so, our purified mixed oils were tolerated by the eyes for a long time (6).

LE CONCEPT :

UTILISATION DES FLUOROCARBURES DANS LA CHIRURGIE DES DECOLLEMENTS DE RETINE

- **LA TECHNIQUE**



Principe d'un tamponnement oculaire par un substitut du vitré.

Fig. 3

- **CHOIX DES FLUOROCARBURES**

-Absence de toxicité

-Absence de pénétration des muqueuses

-Haute densité (d~2)

- **CHOIX DE LA PERFLUORADECALINE**

1989

- **COMMERCIALISATION DE DK-Line**

1991

III – Reactivity of mixed oils : New surfactants preparations

The study of the reactivity of mixed oils was also an interesting challenge because it was possible to imagine the synthesis of new surfactants having :

- a long perfluorinated chain,

or

- two different chains one hydrogenated and the other fluorinated.

Such surfactants would be able to give additives for the preparation of hydrocarbon fire extinguishers (Fig. 4).

The segregation between fluorinated derivatives and the corresponding hydrogenated ones, often account of the difficulty to realize organic synthesis with perfluorinated compounds.

We synthesized new series of molecules with an amide group as polar heads by photoamidation of the corresponding olefins (Scheme III) by the method described by ELAD (7).

With perfluorinated olefins the method does not work in the normal conditions. By modifications of the method : use of large excess of test butanol, we get good results.

The same reactions were carried out in a microscopically heterogeneous medium represented by a nonaqueous microemulsion in which water is replaced by formamide and the olefin and the formamide being both reactants and constituents of the microemulsion (Fig. 5)

- *with terminal olefin* ($C_8F_{17}CH=CH_2$) the amidation, by γ radiolysis, only takes place in a bicontinuous microemulsion and no in direct or reverse micelles. This result can be explained by the easy diffusion of constituents in this structure. On the contrary the olefin diffuses little into the micellar media.

- *with mixed olefin* ($C_8F_{17}CH=CH\ C_{10}H_{21}$) amidation works very well in suitable microemulsions (up to 94 %) and we obtained the opposite regioselectivity to that found in tert-butyl alcohol :

$\frac{a}{b}$ = 7.71 in tert-butyl alcohol

$\frac{a}{b}$ = 0.40 in microemulsions

(Table VI)

This was interpreted in terms of the structure of the microemulsions which anchored the olefin in the interfacial film : the predominantly steric effects in tert-butyl alcohol are thus outweighed by polar effects in the microemulsions (7, 8)

ATOCHEM
Mise au point d'agents extincteurs

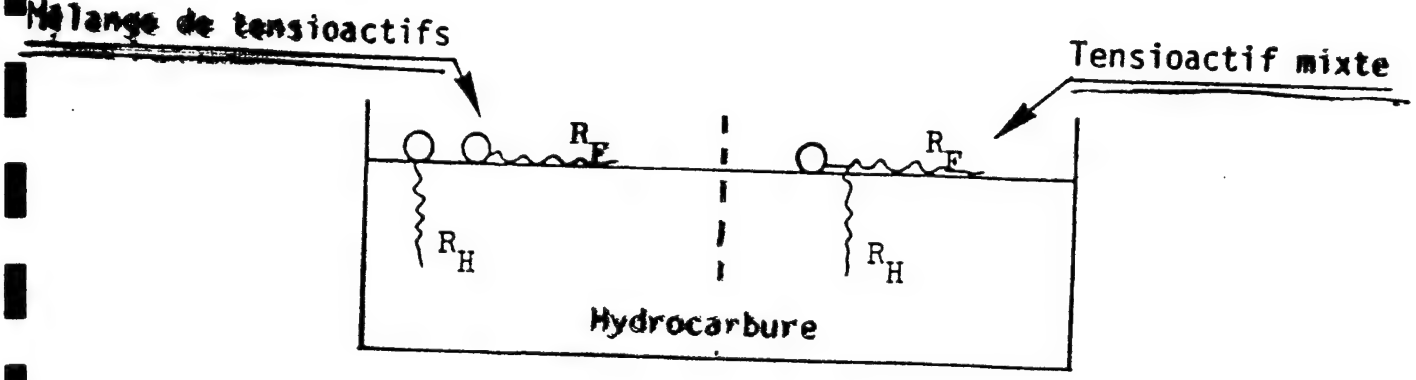


Figure 4

initiation :

$$CH_3COCH_3 \xrightarrow{h\nu} {}^1CH_3COCH_3^* \longrightarrow {}^3CH_3COCH_3^*$$

$$CH_3COCH_3 + HCONH_2 \longrightarrow (CH_3)_2\,C\,OH + CONH_2$$

propagation :

$$R_FCH = CHR_H + CONH_2 \longrightarrow$$

$$R_FCH^{\bullet}-\underset{CONH_2}{CHR_H} + R_FCH\underset{CONH_2}{CH^{\bullet}}-RH$$

$$R_FCH^{\bullet}-\underset{CONH_2}{CHR_H} + HCONH_2 \longrightarrow \underset{CONH_2}{R_FCH_2CHR_H} + {}^{\bullet}CONH_2$$

a

$$R_FCH\underset{CONH_2}{CH^{\bullet}}-RH + HCONH2 \longrightarrow \underset{CONH_2}{R_FCHCH_2R_H} + {}^{\bullet}CONH_2$$

b

termination :

$$2\ {}^{\bullet}CONH_2 \longrightarrow (CONH_2)_2$$ **ethanediamide or oxamide**

Milieu	a/b	Rdt %
t.BuOH	7.7	64
microémulsion	0.4	80
	0.3	85

Schéma III

Figure 4. Structures of the microemulsions (O = oil, W = water, S = surfactant, CoS = cosurfactant).

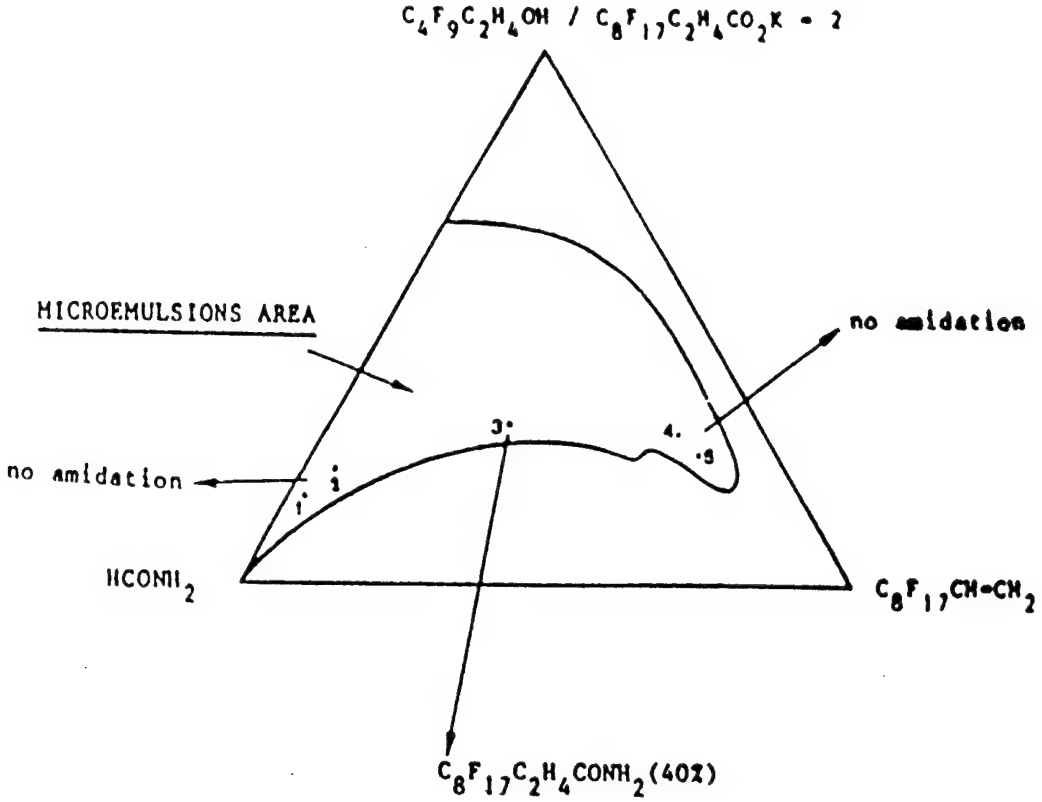


Figure 5. γ radiolysis at 25 °C of microemulsion system ($HCONH_2$, C_8F_{17}-$CH=CH_2$, $C_4F_9C_2H_4OH/C_8F_{17}C_2H_4CO_2K$ = 2).

Table VI. Self-Diffusion Coefficients of $HCONH_2$ (D1) and $C_8F_{17}CH=CH_2$ (D2) in the Microemulsions at 25 °C[a]

	microemulsions (% wt)					
no.	F	O	S	CoS	*D*1	*D*2
1	87	7	2	4	3.62	0.54
2	78	10	4	8	3.37	0.60
3	44	44	4	8	0.85	1.21
4	12	61	9	18	0.60	2.89
5	10	66	8	16	0.60	2.98
		pure $HCONH_2$			5.21	
		pure $C_8F_{17}CH=CH_2$				5.32

[a] F = $HCONH_2$, O = $C_8F_{17}CH=CH_2$, S = $C_8F_{17}C_2H_4CO_2K$, CoS = $C_4F_9C_2H_4OH$. Unit for D = 10^{-10} $m^2 \cdot s^{-1}$ ± 0.08 × 10^{-10} $m^2 \cdot s^{-1}$.

IV – Fluoroalkylglycolipids

1) New Glycolipids

* Synthesis of new glycolipids was an interesting challenge because such compounds can give tubular or helical molecular association and lead to the development of new materials.

** Moreover many glycolipids have been identified as membrane receptors of various bacteria and viruses.

Therefore galactosylceramide (Galcer) whose chemical structure is shown in this picture was identified as an alternative receptor allowing HIV-1 entry into cells of neural and colonic origin. This suggests that analogs of Galcer might have anti HIV activity.

Therefore we synthesized new families of compound having anti HIV activity on CEM cells infected by HIV-1 (Fig. 6) (9,10).

To avoid the detergent effect of compounds **1** we prepared glycolipids **2** and **3**, **3** having a bolaamphiphilic character.

*** Molecules containing fluorinated chains having unusual behavior we synthesized a new series of non-ionic fluorinated compounds derived from lactose, lactobionic acid or gluconolactone.

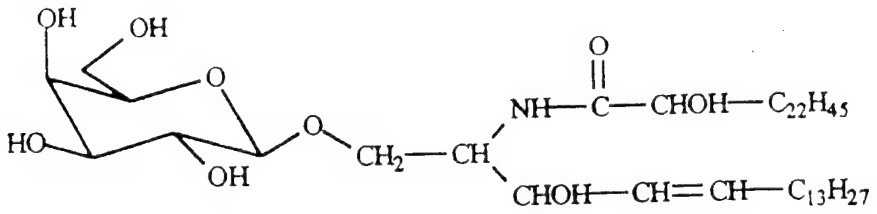
a) Synthesis of new fluorinated non-ionic surfactants derived from lactose and glucose

These derivatives were readily prepared in good yields in an aza wittig reaction from 2-(F-alkyl) ethylazides and the ose or the corresponding acid or lactone (scheme IV) (11).

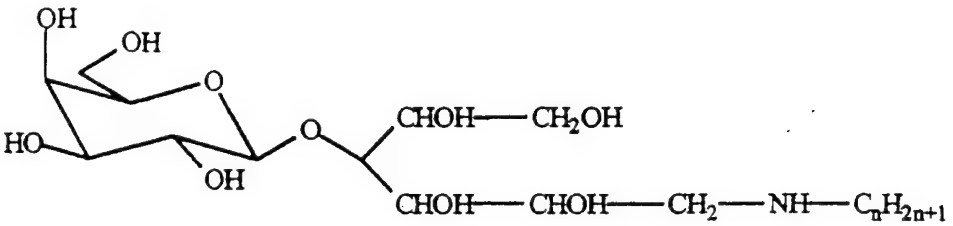
Fluorinated surfactants derived from lactose have good surfactant properties : CMC from 4.3×10^{-5} to 1.9×10^{-3} mol l^{-1}, and very low surface tension at CMC : 15 mN m^{-1} in some cases. But, owing to the instability of hydrocarbons analogs surfactants they are difficult to utilize in biocompatible formulations.

Those derived from lactobionic acid have CMC near 10^{-4} mol l^{-1}, but the surface tension at the CMC is not low enough : they are not good surfactants.

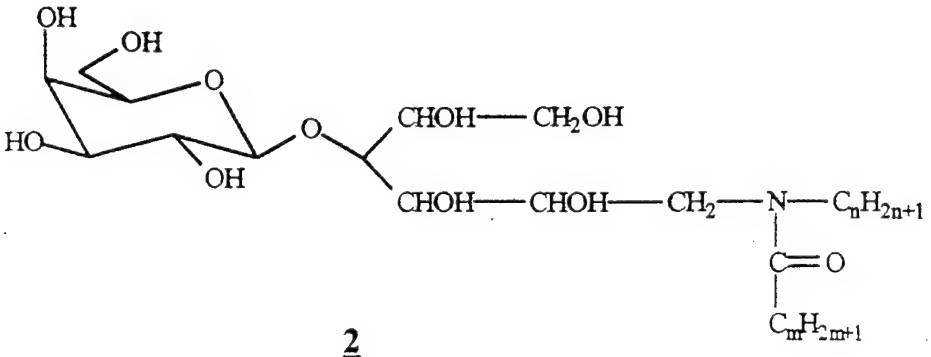
b) Gelification in aqueous and formamide solutions



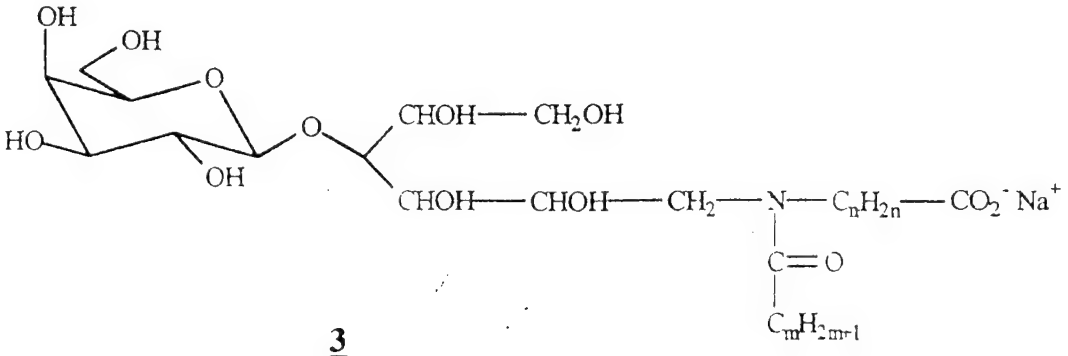
Galcer



1

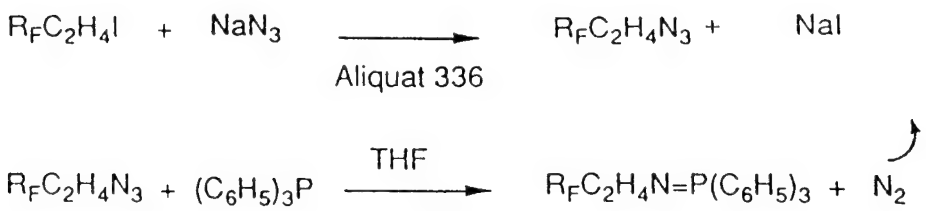


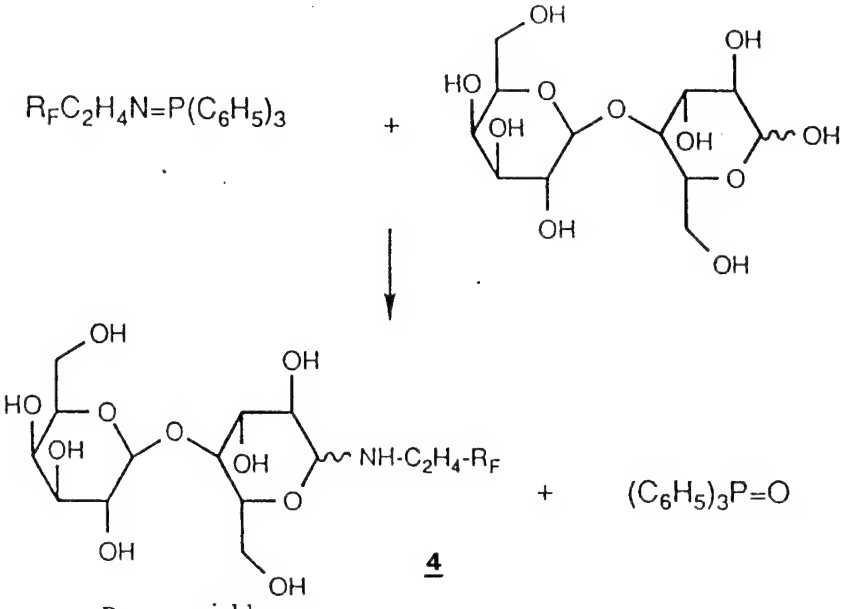
2



3

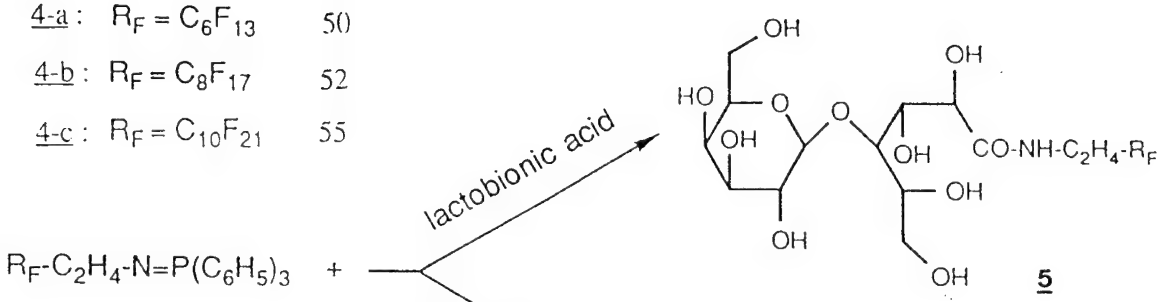
Figure 6





4

	R_F	yields %
4-a :	$R_F = C_6F_{13}$	50
4-b :	$R_F = C_8F_{17}$	52
4-c :	$R_F = C_{10}F_{21}$	55



5

6

	R_F	yields %
5a	C_6F_{13}	90
5b	C_8F_{17}	92
5c	$C_{10}F_{21}$	97
6a	C_6F_{13}	95
6b	C_8F_{17}	95
6c	$C_{10}H_{21}$	95

Scheme IV

N-fluoroalkyllactobionamides having an amide group were able to give gels in water solutions after heating at 100°C and cooling at 0°C with concentrations from 10 to 30 % ($g.ml^{-1}$) depending on the length of the fluoroalkyl chain.

N-fluoroalkylgluconamides are insoluble in water, but it was possible to study their gelification properties in formamide after heating them at 155°C and cooling at O°C : **it was the first study of gels in formamide** (12).

c) Bolaamphiphilic compounds

We also prepared bolaform compounds analogous of hydrocarbon derivatives (schema V). In general amphiphiles of this type form vesicles or micelles or both.

The aggregates formed with compound **3b** (n=11) were spherical vesicles of polydispersed sizes with a maximum diameter around 200 nm (Fig. 6).

Compound **3a** (n=10) unexpectedly formed 17 nm thick filaments (Fig. 7) consistent with the findings of LUISI that slight alteration in the lipid part of the monomer may give rise to marked changes in architecture of the aggregates formed in solution.

2) New Catanionic glycolipids

Catanionic surfactant mixtures such as two-chain or gemini, have received increasing attention. showing various aggregates microstructures (micelles, vesicles, lamellar phases).

We reported the synthesis of new analogs of Galcer replacing the amide covalent bond by an amine-acid ionic bond (Fig. 8) we thus obtained new catanionic glycolipids in high yields (96 % in two steps from unprotected lactose).

These new catanionic glycolipids showed interesting anti HIV-I activities acting as monomeric analogs of Galcer (13). They were characterized by their surface active properties, lamellar mesophases and by their aptitude to spontaneouly form vesicles (14).

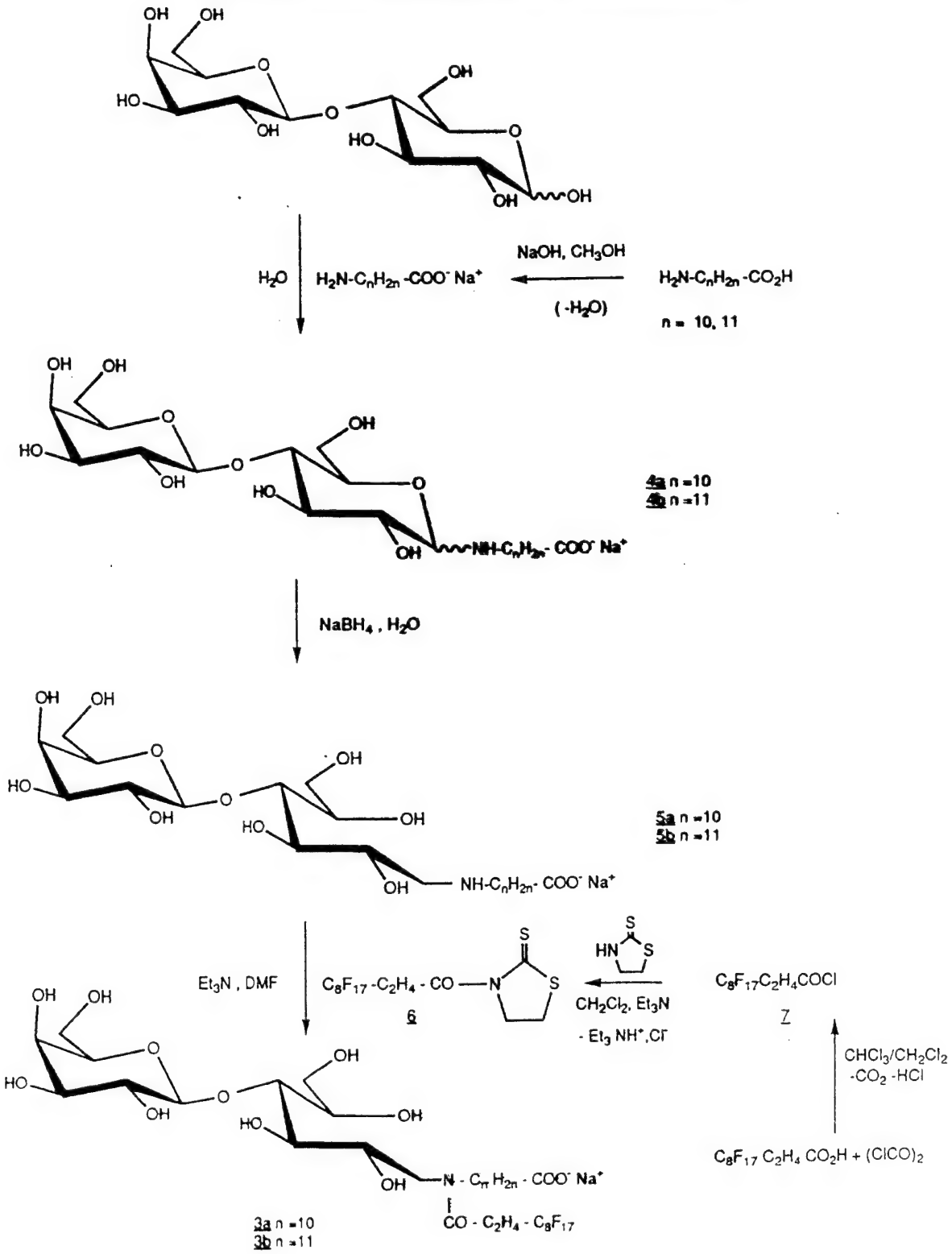
A) Double chain fluorocarbon/hydrocarbon compound

The fluorocarbon chain being stiffer than a hydrocarbon we decided to mix two surfactants, one hydrogenated and the other fluorinated to prepare a new mixed double chain catanionic derivatives by mixing, in water at room temperature, one equivalent of hexadecylaminolactitol with an equivalent of perfluorooctyl propanoic acid (scheme VI)

Infrared spectroscopy indicates a structure similar to that of the hydrogenated catanionic compounds, indeed the strong hydrophobic properties of both chains can favor their association in spite of the lipophobic character of the fluorinated one [The NMR characterisation in water is impossible, because the high aggregate stiffness prevents atomic relaxation and gives very broad signals]

Self association properties (Figure 9)

Synthesis of *N*-(ω-(Sodium oxycarbonyl)alkyl)-*N*-(perfluoroalkylethylcarbonyl)-1-amino-1-deoxylactitol (3a,b)



Scheme V

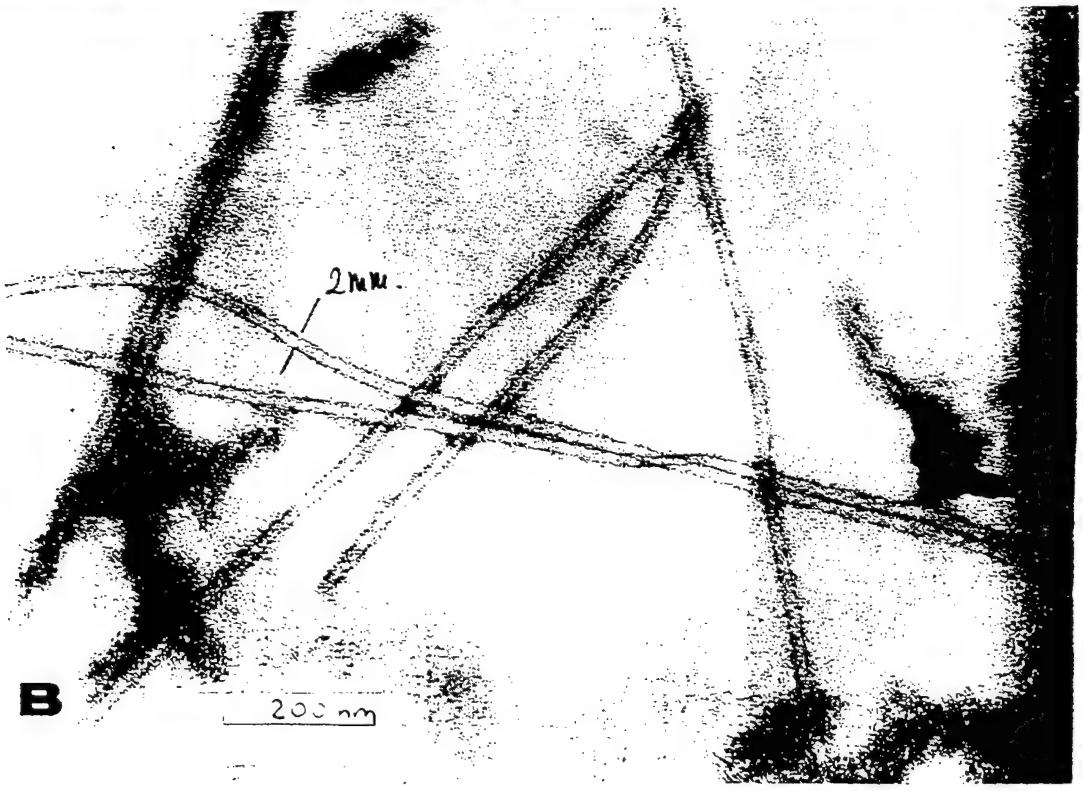
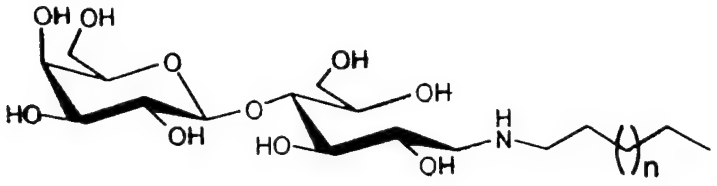
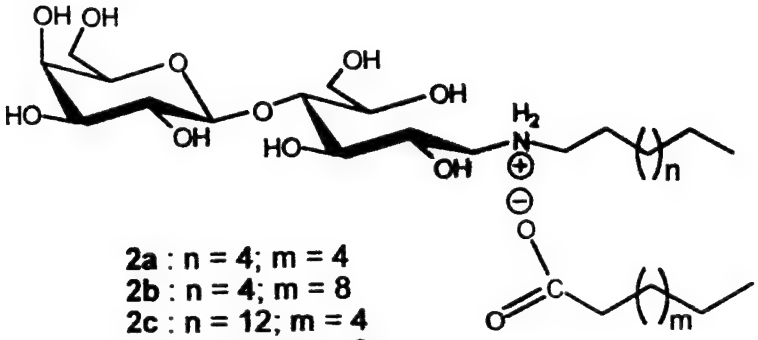


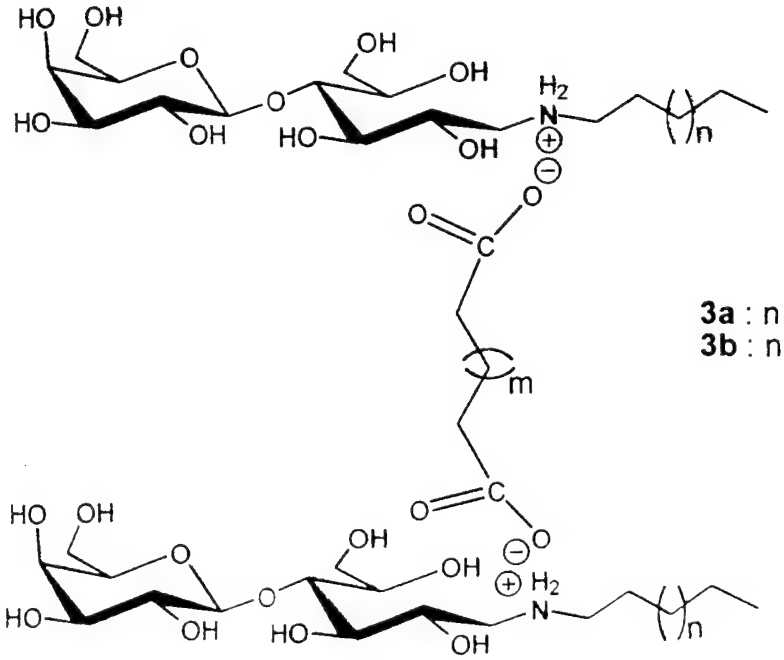
Figure 5. 7



1a : n = 4
1b : n = 12



2a : n = 4; m = 4
2b : n = 4; m = 8
2c : n = 12; m = 4
2d : n = 12; m = 8



3a : n = 4; m = 10
3b : n = 12; m = 10

Fig. 8

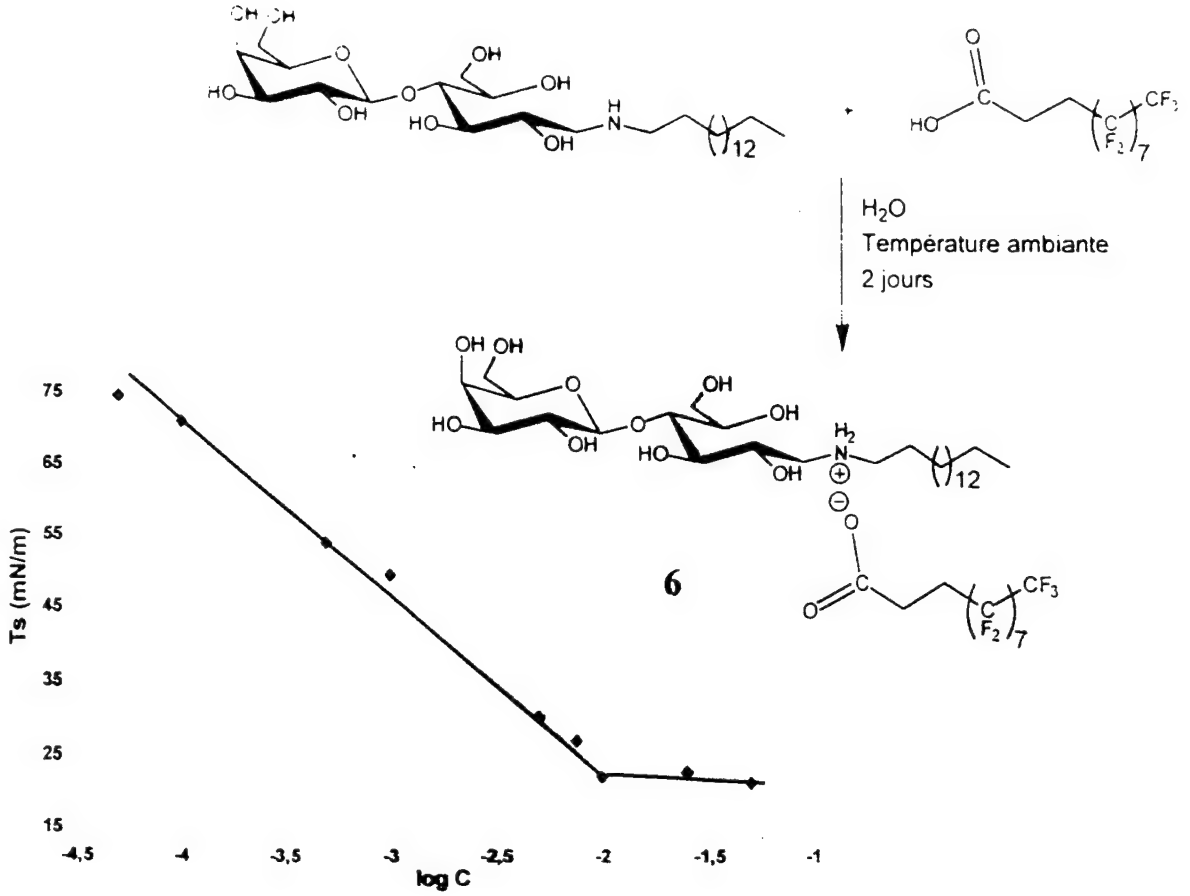
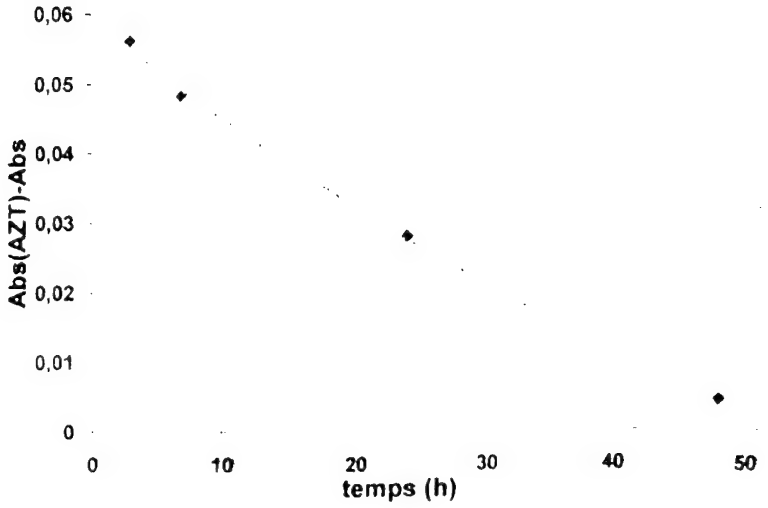


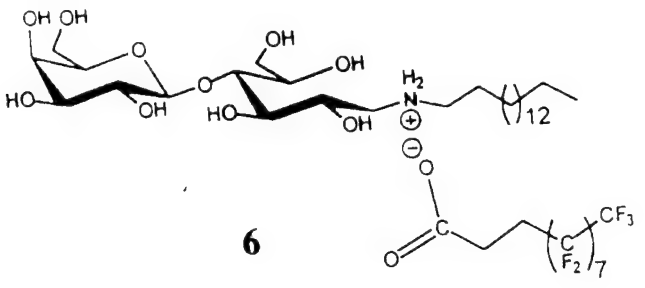
Figure 52 : Concentration d'agrégation critique du composé 6

Solution (rapport molaire)	Absorbance [AZT témoin]	Absorbance	$AZT_{encapsulé}$ (%)
6/AZT : 10/1	0,499	0,469	6
6/AZT : 20/1	0,517	0,470	10

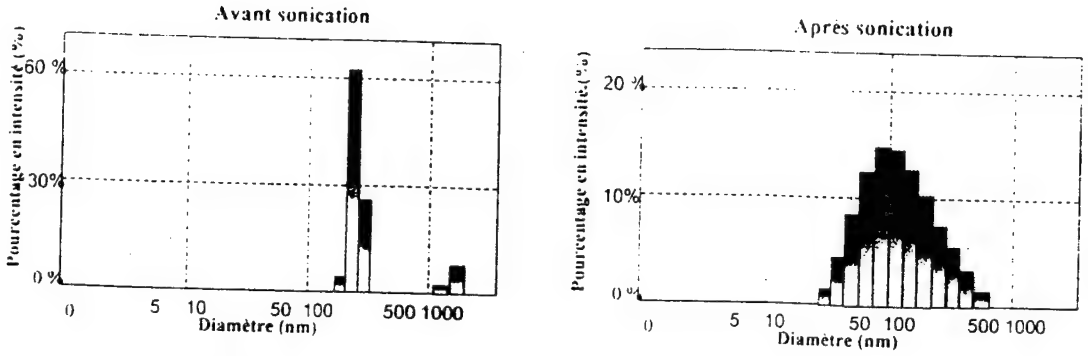
Tableau 3 : Taux d'encapsulation de l'AZT à 37 °C



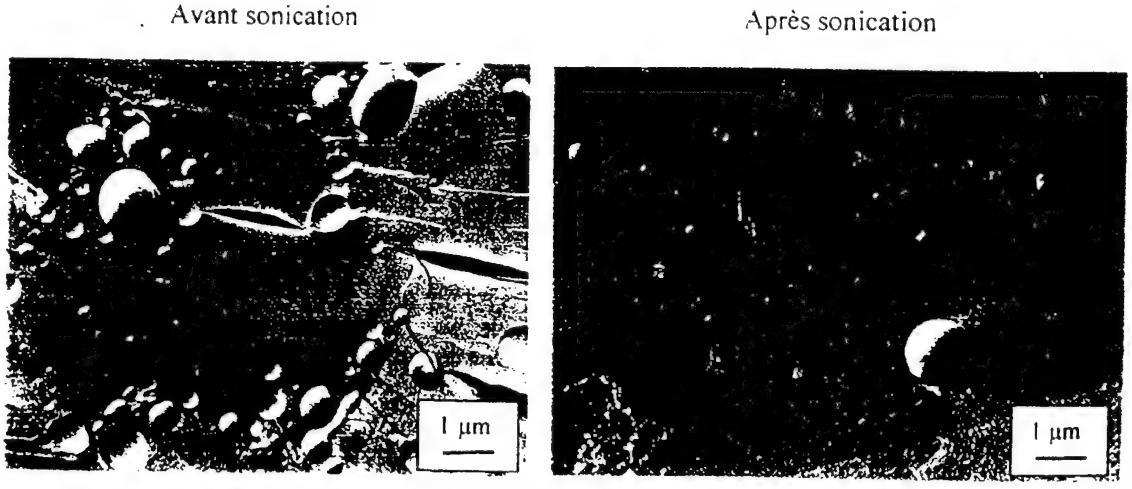
Relargage de l'AZT en fonction du temps à 37 °C



6



Distribution de taille des objets formés par 6 avant et après sonication à 25°C



Vésicules formées par 6 avant et après sonication (cryofracture)

In aqueous solution, at 25°C, compound **6** has a Critical Aggregation Concentration which is higher than that usually observed with fluorinated surfactants.

The **fluorinated chain** lipophobicity may explain a low segregation between hydrogenated and fluorinated chains allowing us to visualize the cmc of one part of the free surfactants. Then, in this case, the true surfactants concentration is lower than the whole concentration because only a small proportion of catanionic derivative is not associated.

Dynamic light scattering shows the **spontaneous** formation of **two populations of large objects** centered at 250 nm and 1.5 µm. By **sonicating** the solution, these populations disappear and we observe a new polydisperse Gaussian one centered at 130 nm. (Figure 10).

The aggregate morphology determined by freeze fracture replica is in agreement with the results previously observed by dynamic light scattering. In addition we observe giant vesicles, spontaneously formed in water, a very low proportion of them persisting after sonicating the solutions.

As the vesicles were stable for more than 3 hours, they were used to encapsulate AZT.

b) AZT Encapsulation

The quantity of encapsulated AZT in vesicles was measured before and after sonicating solution, having molar ratio $\frac{6}{AZT}$ = 10/1 and 20/1

In all cases the desired results were not obtained without sonicating. With sonicated samples, 6 to 10 % AZT was encapsulated and maintained in the vesicles for 3h. The curve shows the gradual release of AZT over 48 hours (Table VI and Fig. 11).

The encapsulation was only possible in sonicated vesicles and not in spontaneous vesicles, because objects after sonicating have **size closely related to that of liposomes** and they are much more numerous than those spontaneously formed ; there is also greater permeability to AZT of the spontaneous vesicles.

c) Anti HIV activity

The catanionic compounds synthesized are both analogs of galactosylceramide and are amphiphilic derivatives suitable for the formulation of other anti HIV compounds.

Fluorinated analogs have a behavior very different from the hydrocarbon analogs : for an equivalent lipophilicity :

* the cytotoxicity is lower...but ...
* the inhibitor activity is obviously lower !

"substitution of a hydrocarbon chain by a fluorocarbon one diministres the activity"

Moreover the CC50 is 400 times lower than its CAC revealing its high toxicity both for the monomer and the aggregate.

In these conditions it is difficult to use this compound to carry active substances.

B) gemini catanionic derivative

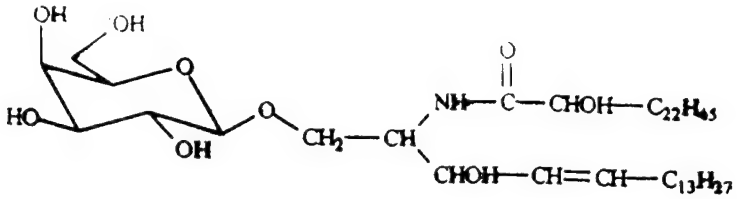
Happily, gemini cationic derivative **3b** is much more effective than the best covalent analog CA52. This gemini derivative presents a very low cytotoxicity : the cytotoxic concentration is at least 10 times higher than its CAC ; consequently aggregates of this compound are not toxic.

Encapsulation of AZT : we make an AZT formulation with the gemini 3b : both AZT and 3b have an anti HIV activity but not at the same moment in the replication cycle.

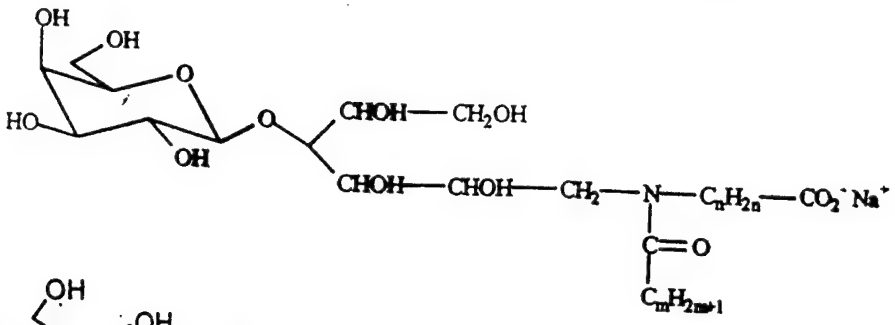
Neither of the formulation were toxic in the concentration range tested on CEM-SS cells.

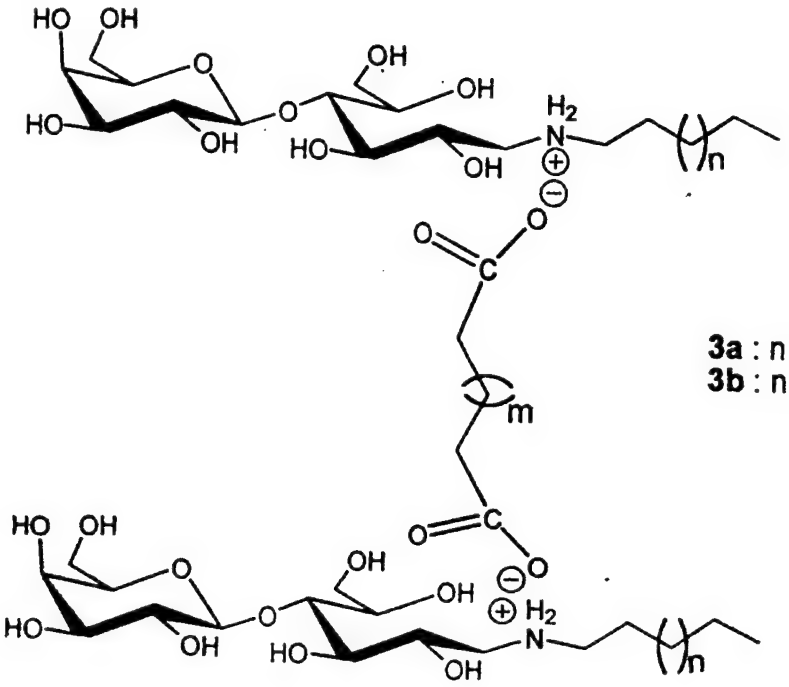
It is obvious that there is a strong synergistic effect in vitro with the two substances associated.

GalCer



CA 52





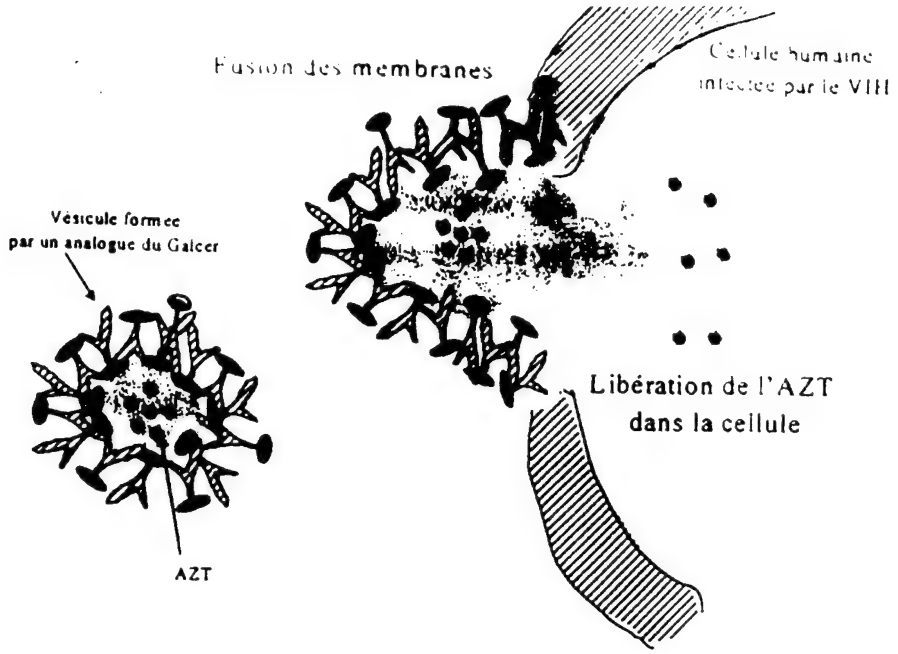
3a : n = 4; **m = 10**
3b : n = 12; **m = 10**

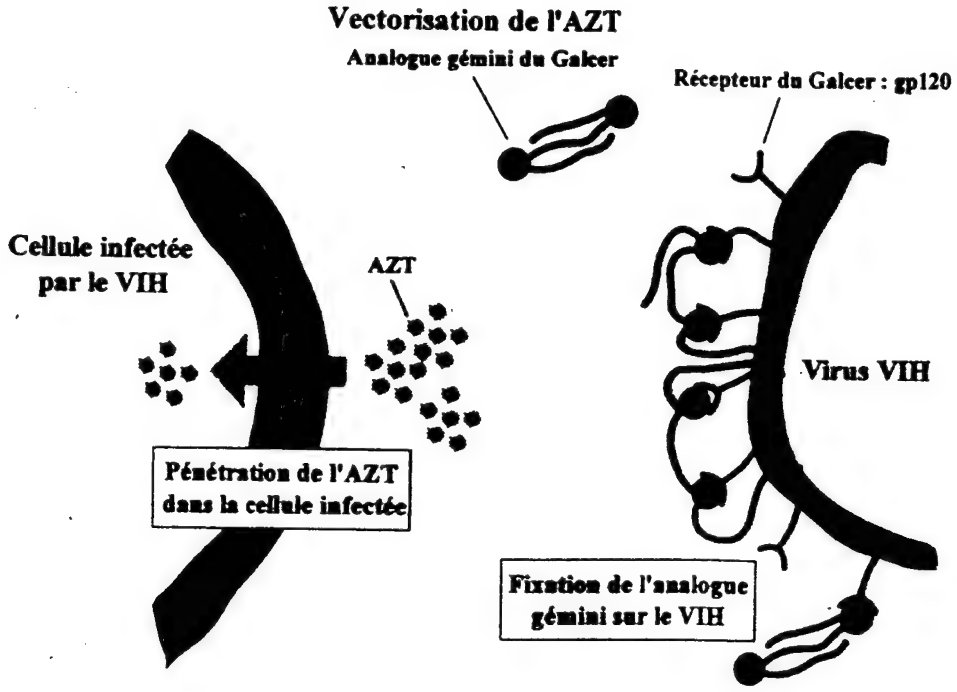
Composés	n	m	IC_{50} (µM)	CC_{50} (µM)	IS	CAC (µM)	Log P
3a	4	8	500	600	1,1	2500	2,1
3b	12	8	0,5	> 100	> 200	10	8,4
CA52	10	15	50	220	4,5	138	4,5

Résultats biologiques des analogues catanioniques gémini

Formulation	IC_{50} (µM)	[AZT] (µM) à IC_{50}	CC_{50} (µM)	IS
3b/AZT : 100/1	0,25	0,0025	> 10	> 40
3b/AZT : 500/1	0,05	0,0001	> 10	> 200
3b	0,5	-	> 100	> 200
AZT	0,006	0,006	> 1	> 166

Résultats biologiques de formulations de l'AZT





Stratégie de la formulation de l'AZT avec l'analogue gémini **catanionique 3b**

Formulation	IC_{50} (µM)	[AZT] (µM) à IC_{50}	CC_{50} (µM)	IS
3b/AZT : 100/1	0,25	0,0025	> 10	> 40
3b/AZT : 500/1	0,05	0,0001	> 10	> 200
3b	0,5	-	> 100	> 200
AZT	0,006	0,006	> 1	> 166

Résultats biologiques de formulations de l'AZT

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AMPHIPHILIC TELOMERS CONTAINING VINYLIDENE FLUORIDE BASE-UNITS

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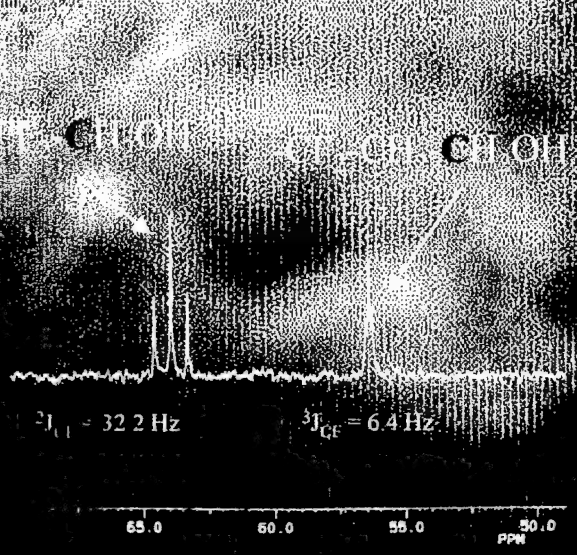
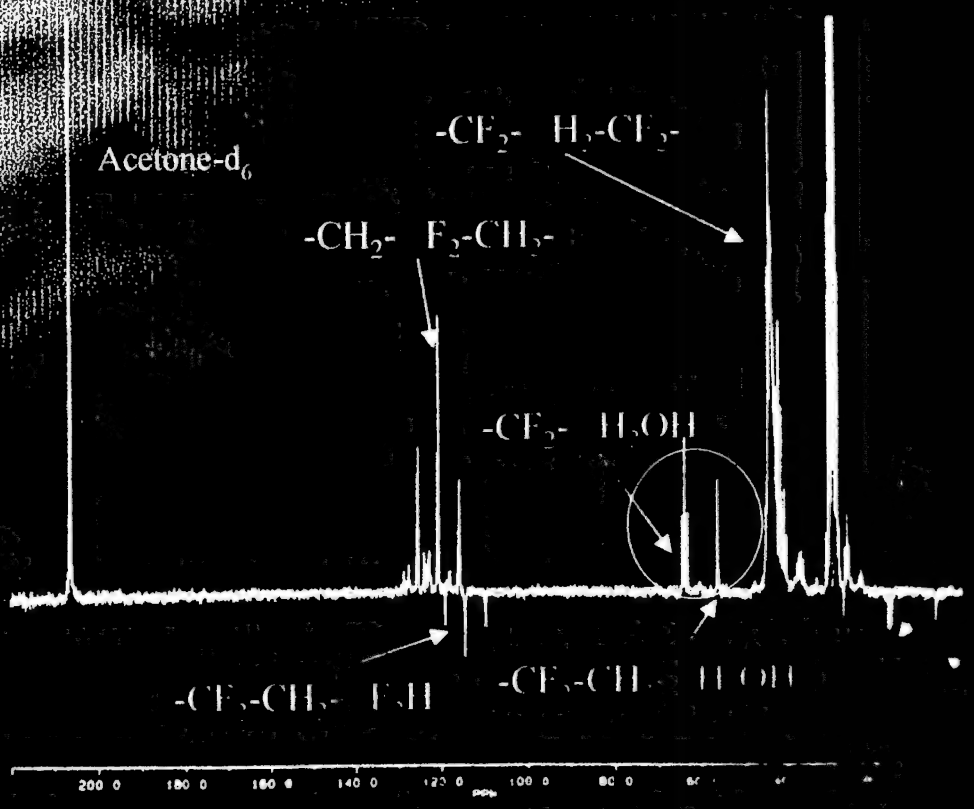
CONTENT

Regioselectivity

- [illegible] selective addition of hydroxymethyl $*CH_2OH$ radic[illegible]
- [illegible] functional telomers from direct addition of radical to VDF

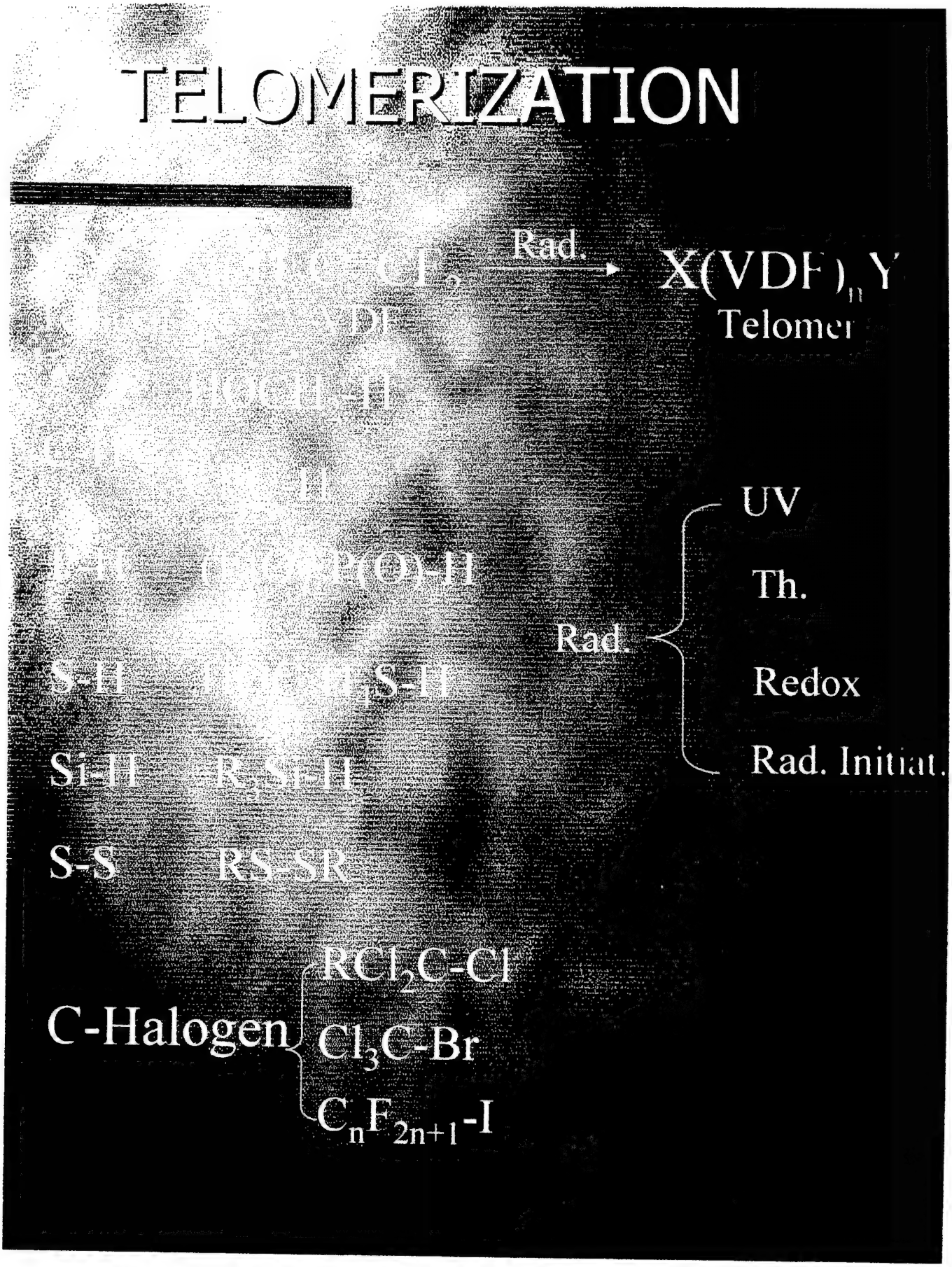


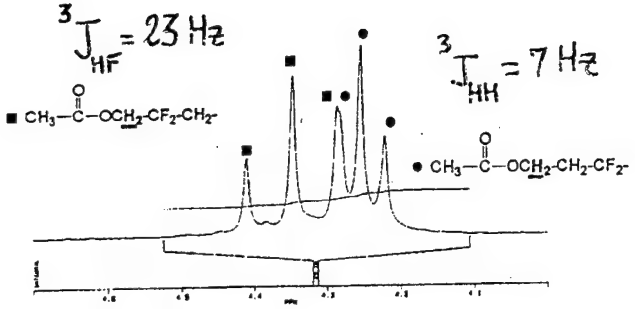
Expansion of region
[illegible]roxyl functions



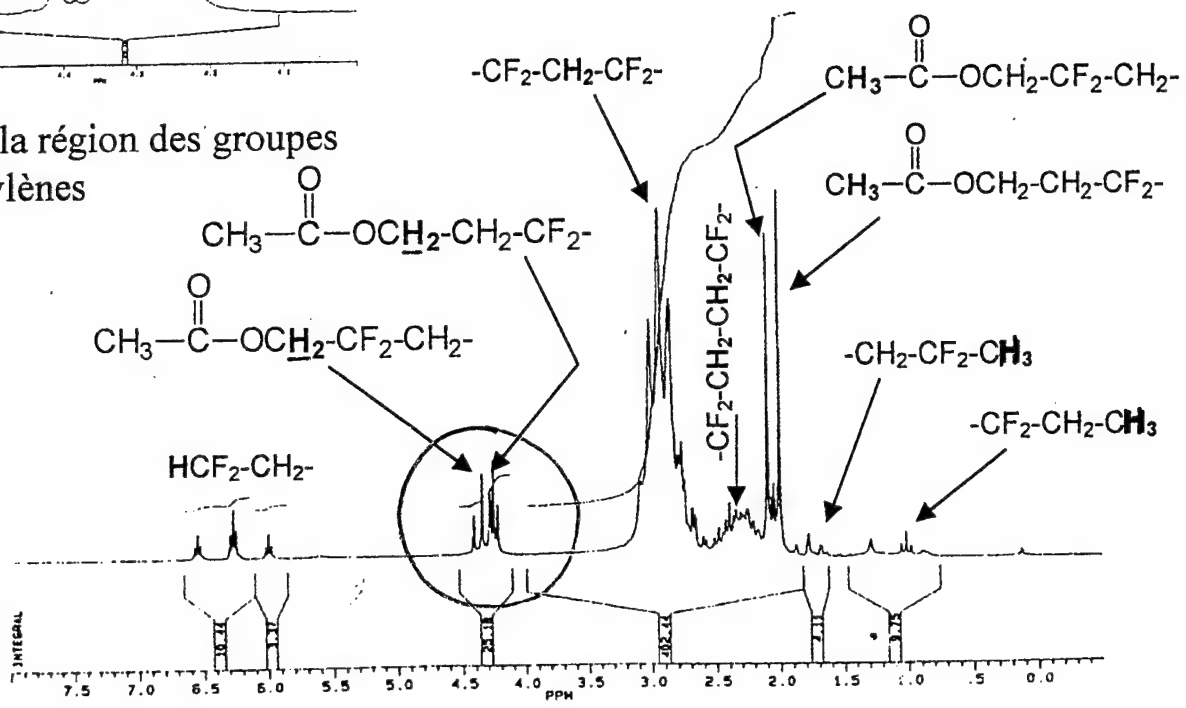
[illegible] NMR spectrum of VDF [illegible]OH telome[illegible]

TELOMERIZATION



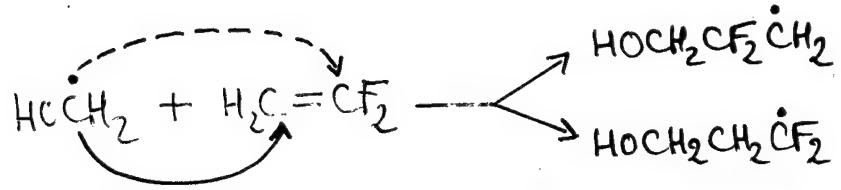


Expansion de la région des groupes hydroxyméthylènes



Spectre RMN ^{1}H des télomères VDF-MeOH ($\overline{DP_n}$ = 10.8) après acétylation par le chlorure d 'acétyle

PM3



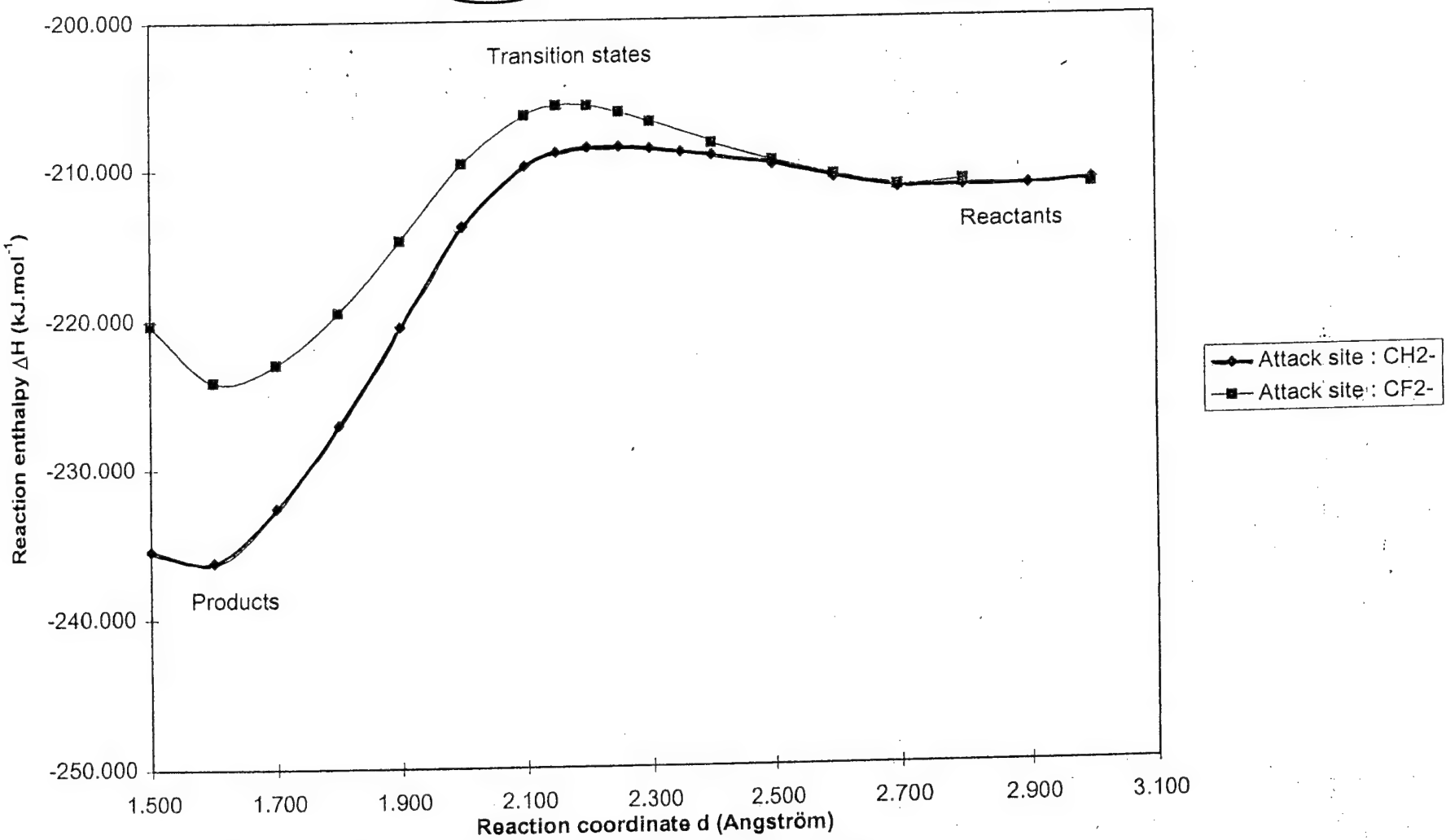
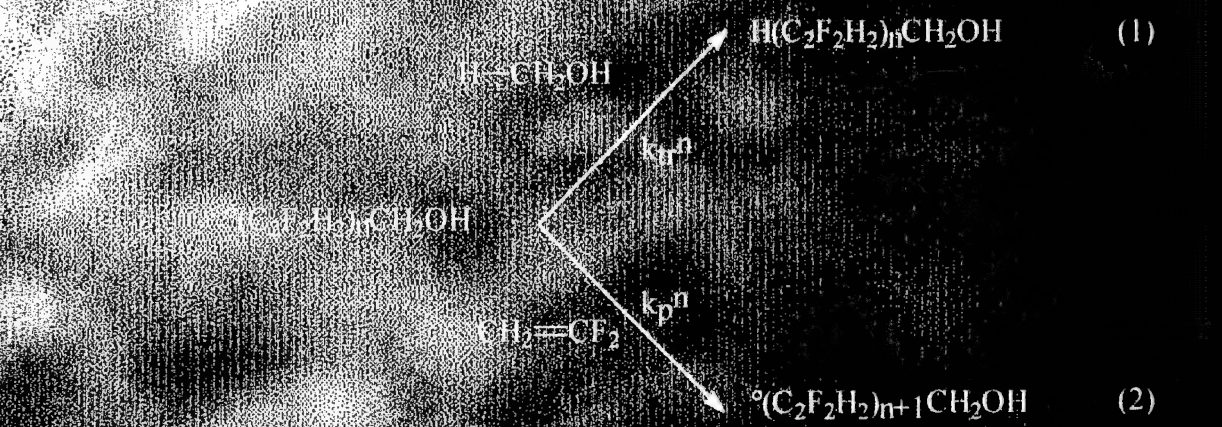


Figure 4 : Reaction pathways of the addition of the hydroxymethyl radical on VDF

Kinetic Study of Telomerization

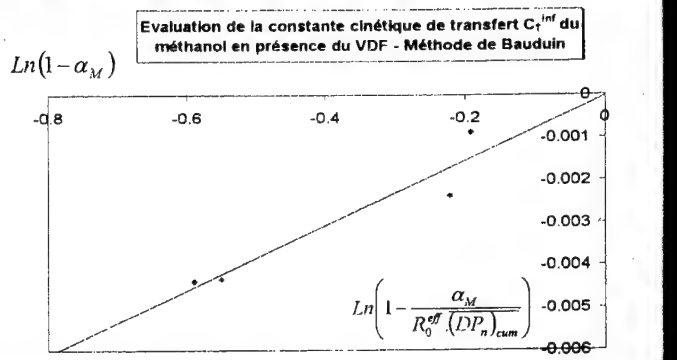


Transfer Constant (coefficient) : $C_T^n = \frac{k_{tr}^n}{k_p^n} \xrightarrow{n \geq 3 \text{ or } 4}$ (

Bauduin equation :

$$Ln\left(1 - \frac{\alpha_M}{R_0^{eff}.(DP_n)_{cum}}\right) = C_T.Ln(1-\alpha_M)$$

$\Rightarrow$ **C_T^{∞} = 8.10^{-3} at 140°C**



TELOMERIZATION OF FLUOROOLEFINS WITH MeOH

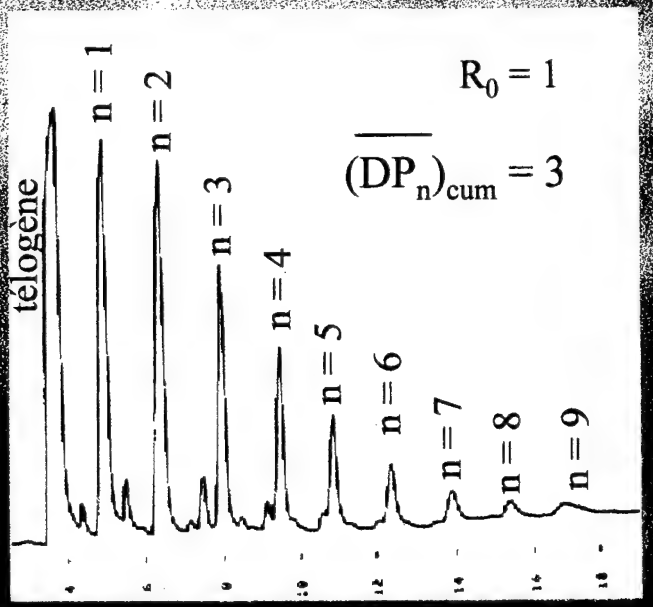
OLEFIN	INIT. COND.	$\overline{DP}_n$	C_T	REF.
$F_2C=CF_2$	AIBN / 70°C	1-4	0.150	Kostov et al. (1998)
$F_2C=CFCF_3$	Th, UV or peroxide	1	n.d.	Haszeldine et al. (1985)
$F_2C=CFCl$	$(tBuO)_2$, γ-rays or UV	1-3	n.d.	Liska (1970)
$F_2C=CFH$	γ-rays	5	n.d.	Powell and Chambers UK Pat. 2292151 (1996)
$F_2C=CH_2$	$(tBuO)_2$/140°C	8-12	0.008	This work

C_T^∞ du diéthylphosphite

faibles masses molaires

Peroxyde de di-t-butyle

$$H\text{-}P(O)(OEt)_2 + n\ CH_2{=}CF_2 \xrightarrow[T_R = 140°C]{} H(VDF)_nP(O)(OEt)_2$$



Chromatographie en phase gaz d 'une distribution de télomères VDF-diéthylphosphite

$$F_n = \frac{C_T^n . R}{\prod_{j=1}^{j=n} (C_T^j . R + 1)}$$

F_n = fraction molaire de l 'adduit d 'ordre n

Théorie de DAVID et GOSSELAIN

$\Rightarrow$ **$C_T^\infty = 3{,}8.10^{-1}$ à 140°C (en solution dans MeCN)**

- $\overline{(DP_n)}_{cum}$ des télomères ajustables selon les conditions expérimentales

$(\overline{(DP_n)}_{cum} = f(T_R, [\text{réactifs}], \text{co-solvant}))$

	n = 1	n = 2	n = 3	n = 4	n = 5	n = 6
C_T^n	0,256	0,375	0,375	0,376	0,378	0,378

Tableau 10 : Valeurs des constantes de transfert C_T^n du diéthylphosphite avec le VDF pour les ordres de 1 à 6.

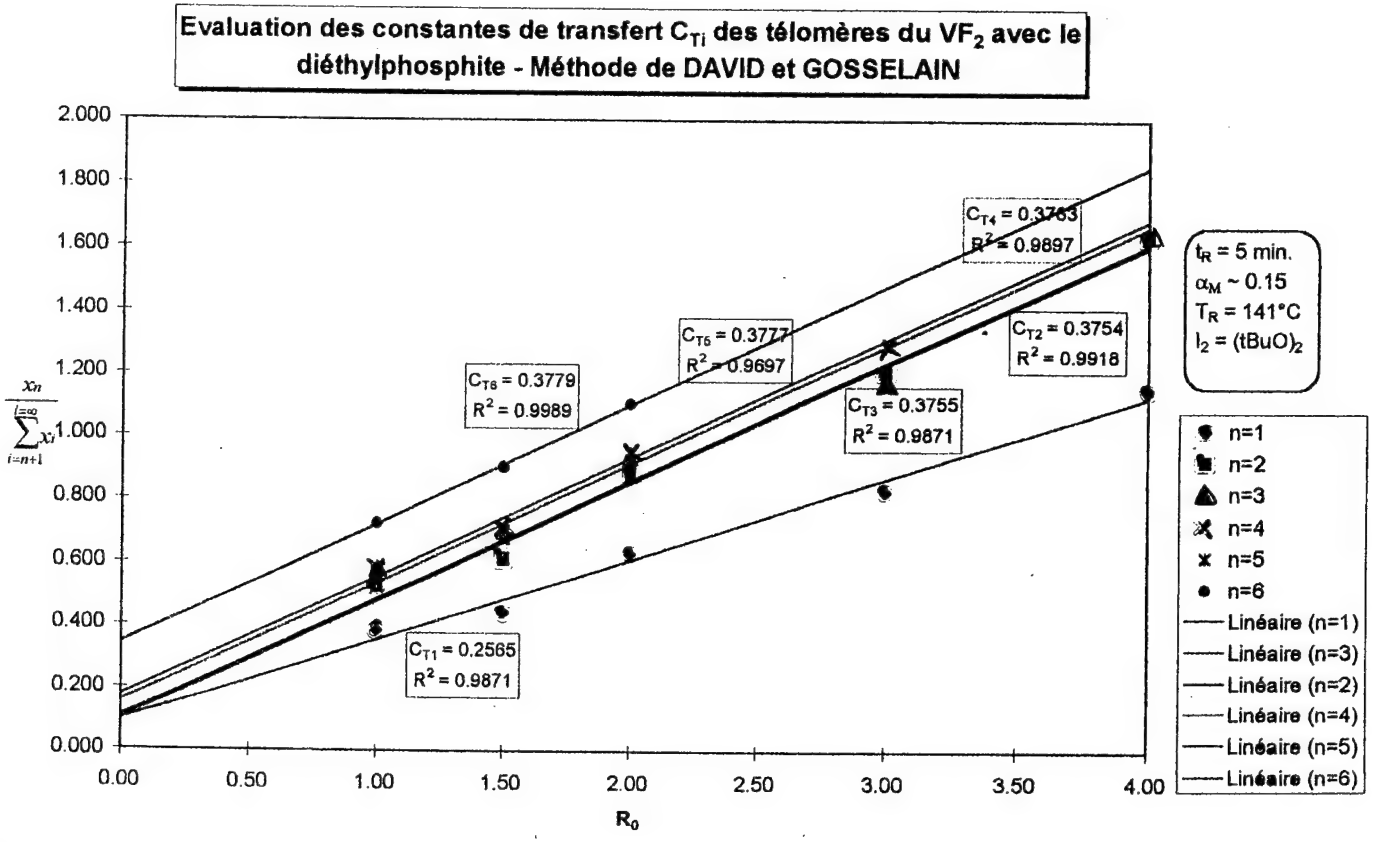
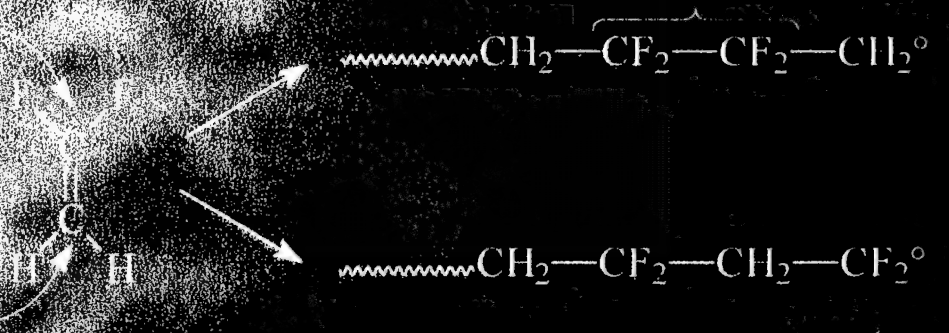


Figure 22 : Evaluation des constantes de transfert C_T^n des premiers ordres, caractéristiques de la télomérisation radicalaire du VDF avec le diéthylphosphite, en solution dans l'acétonitrile, à 140°C.

Défauts d'enchaînements

Télomérisation du VDF-$HP(O)(OEt)_2$

défaut d'enchaînement t-t



- Monoadduit : $HCF_2CH_2P(O)(OEt)_2$ — 100 %
- Diadduit : $HCF_2CH_2CF_2CH_2P(O)(OEt)_2$ — 86,5 %
  $H_3C\quad CH_2P(O)(OEt)_2$ — 13,5 %
- Triadduit : $HCF_2CH_2CF_2CH_2CF_2CH_2P(O)(OEt)_2$ — 90,8 %
  $H_3C\quad CH_2CF_2CH_2P(O)(OEt)_2$ } 9,2 %
  $H_3CCF_2CH_2\quad CH_2P(O)(OEt)_2$ }
- Hauts télomères ($\overline{(DP_n)}_{cum} \sim 20$) : défauts t-t et q-q — 10 %

(Taux de RMN ^{19}F)

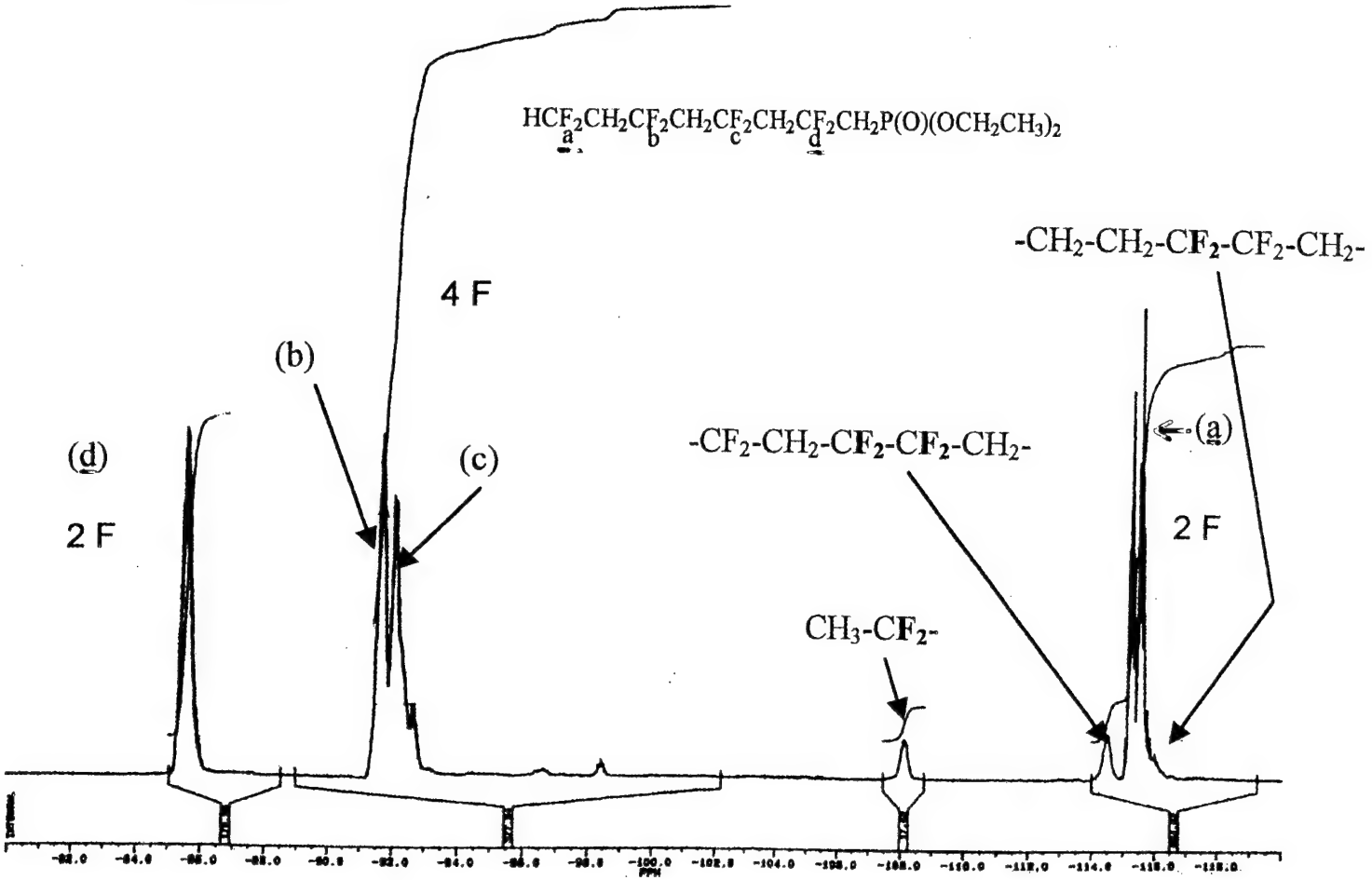


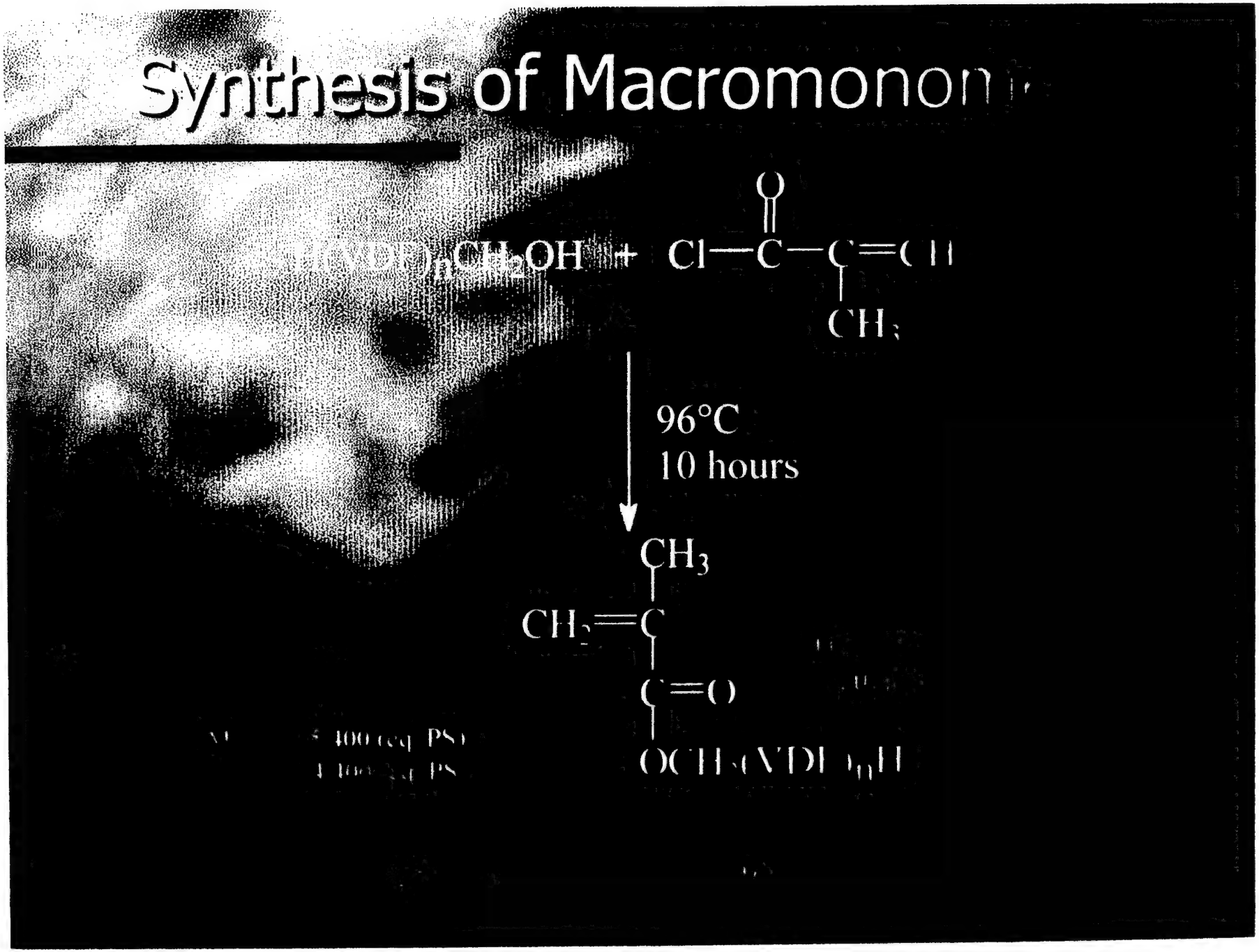
Figure 18 : Spectre RMN ^{19}F du tétradduit 4 $H(VDF)_4P(O)(OEt)_2$ de la télomérisation du VDF avec le diéthylphosphite.

C_T - BDE RELATIONSHIP

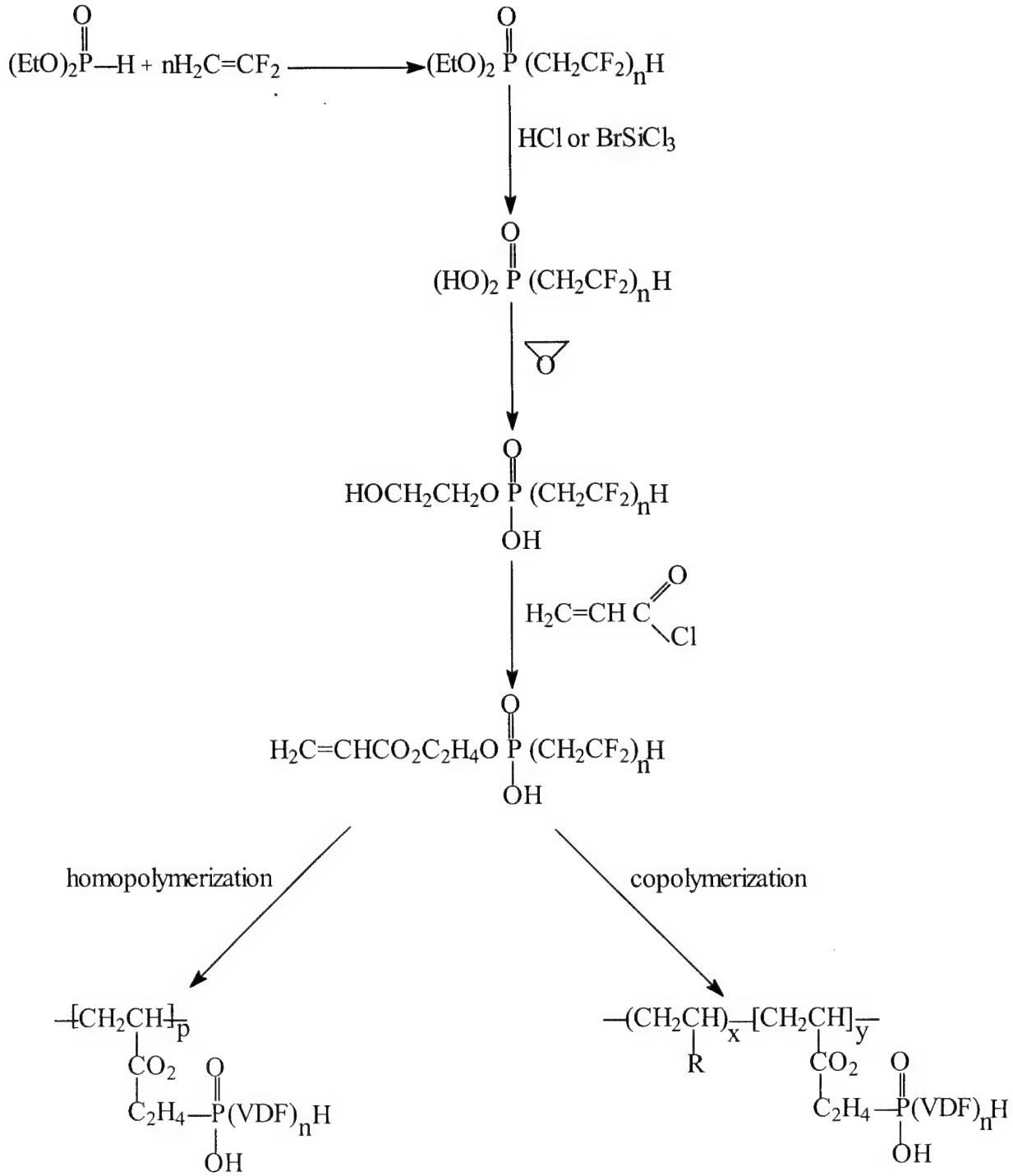
$$X\text{–}Y + H_2C{=}CF_2 \xrightarrow[140°C]{(tBuO)_2} X(C_2H_2F_2)_nY$$

Transfer agent	C_T	BDE (kJ/mol)
$H\text{-}CH_2OH$	0.008	411
$H\text{-}CCl_3$	0.060	393
$Cl\text{-}CCl_3$	0.250	306
$H\text{-}P(O)(OEt)_2$	0.350	322 (?)
$Br\text{-}CCl_3$	> 30	234
$H\text{-}SC_2H_4OH$	> 40	< 340 (?)
I-Cl	Very high	208

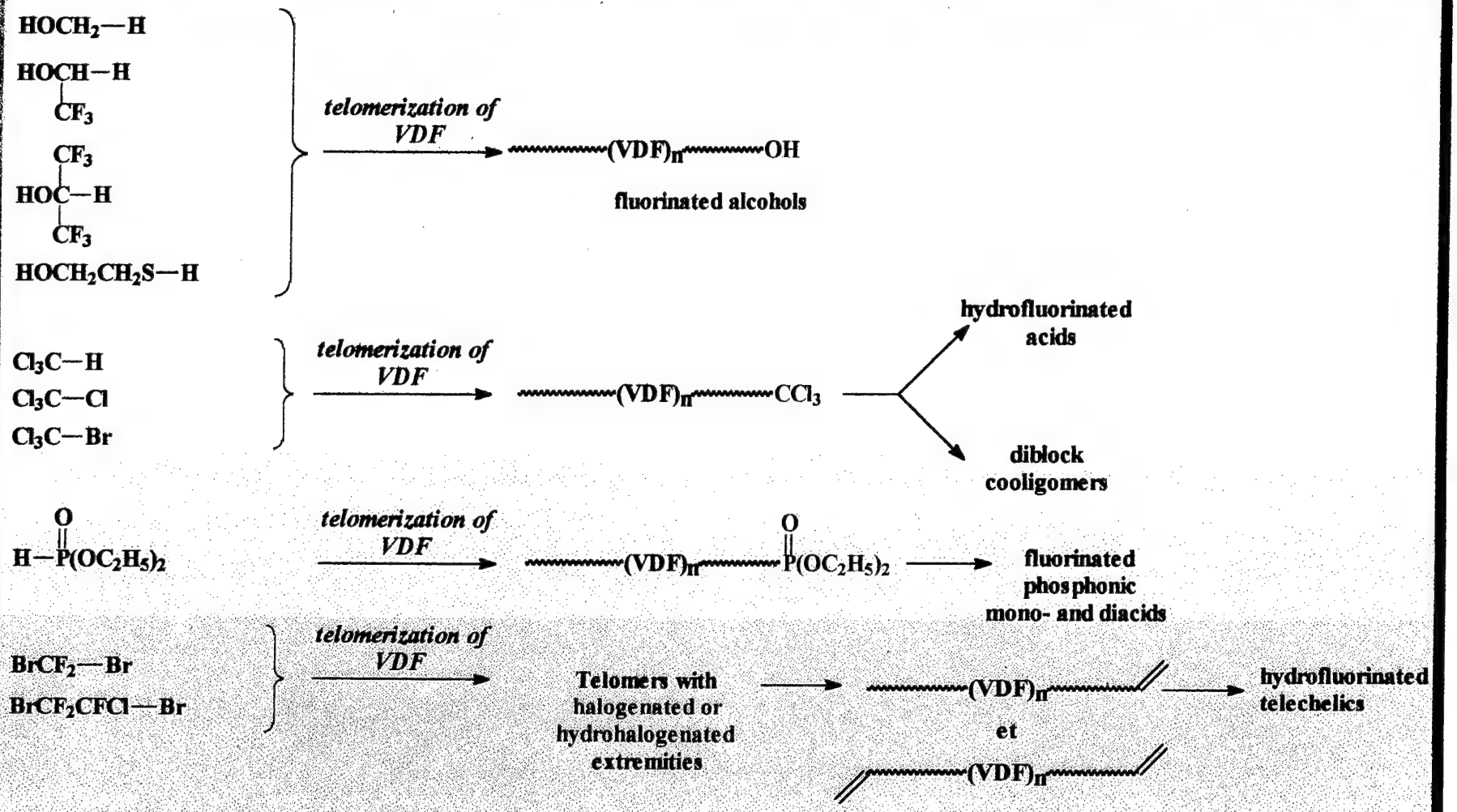
Synthesis of Macromonomer



POLYMERIZABLE SURFACTANTS



Fulfilled reactions



ACKNOWLEDGMENTS

COMPANIES

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RESEARCHERS

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Dr BOULAHIA

Dr DUC

Mr KHARROUBI

Dr MANSERI

Dr RATSIMIHETY

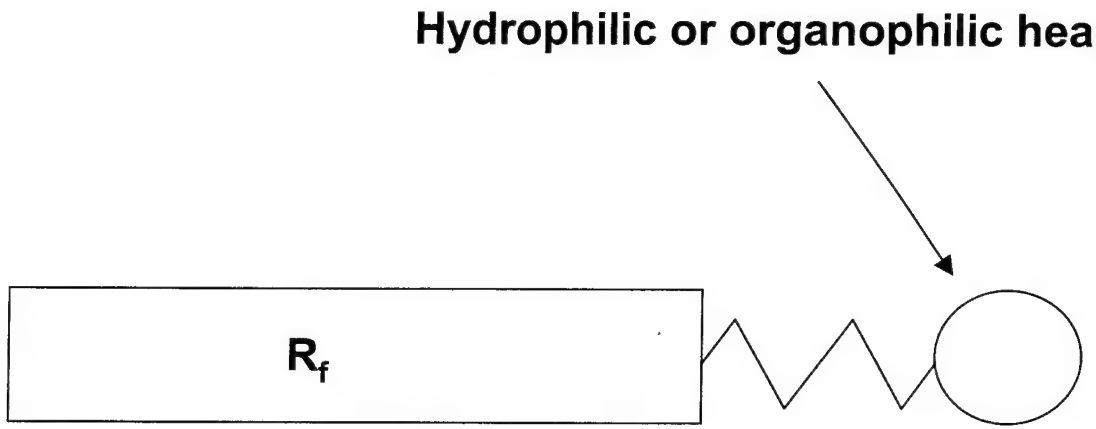
FLUORINATED SURFACTANTS

IN FIRE FIGHTING FOAMS

Martial PABON

ATOFINA
Centre d'Application de Levallois
Service Agents d'interfaces

Structure of a fluorinated surfactant



Linear or branched perfluorinated chain
Ex. : C_nF_{2n+1}-

Hydrophobic and oleophobic chain

Spacer

FLUORINATED SURFACTANTS IIN FIRE FIGHTING FOAMS

- Synthesis
  - Fluorinated part of the surfactant
    - Electro fluorination
    - Telomerization

- Characteristics of perfluorinated carboxybetaïne
  - Surface tension in water
  - Phase diagram

- Fire fighting foams (solvent fires)

- Polymeric additives for fire fighting foams

- Conclusions

INDUSTRIAL PROCESS

Electro fluorination

Raw material:
Alkyl acid chloride
or alkyl sulfochloride

Rather simple installations

Low yield

Branched fluorinated chain

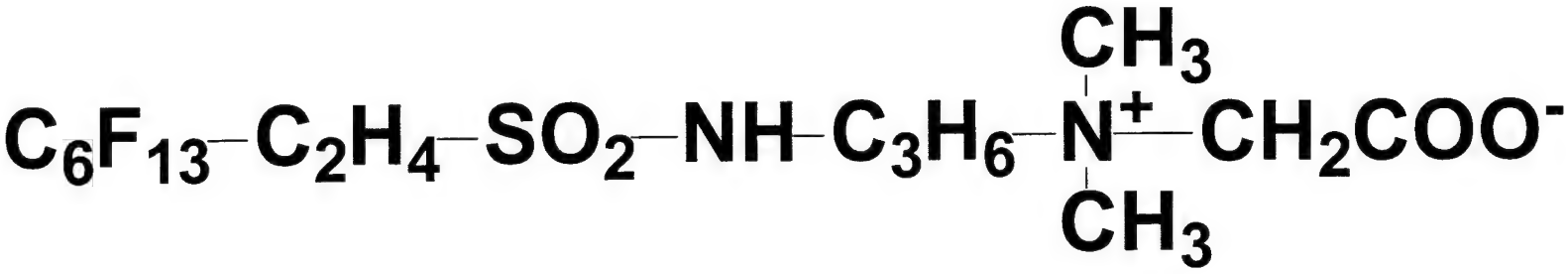
Telomerization

Raw material:
Tetrafluoroethylene
and iodine

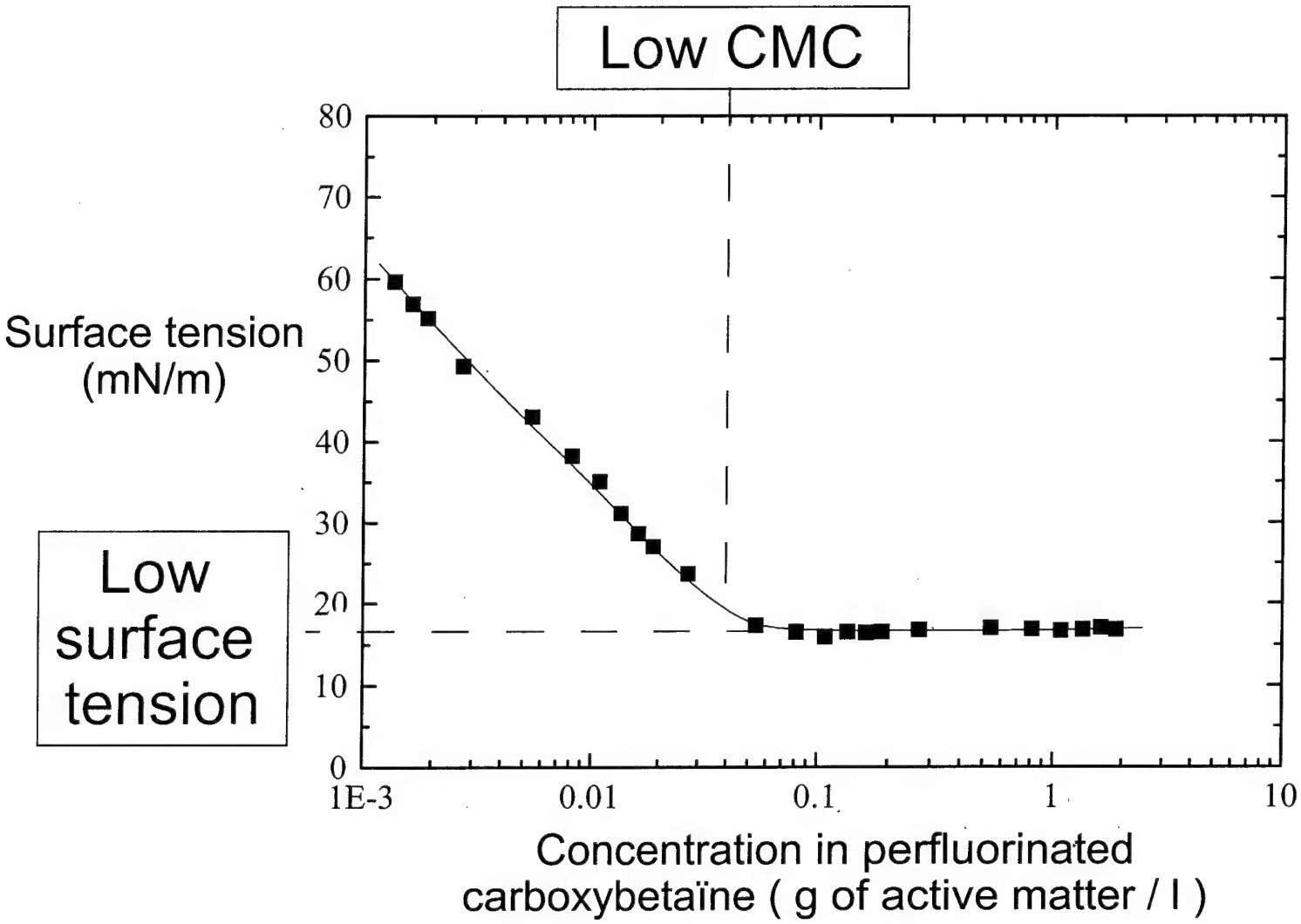
High yield

Linear fluorinated chain

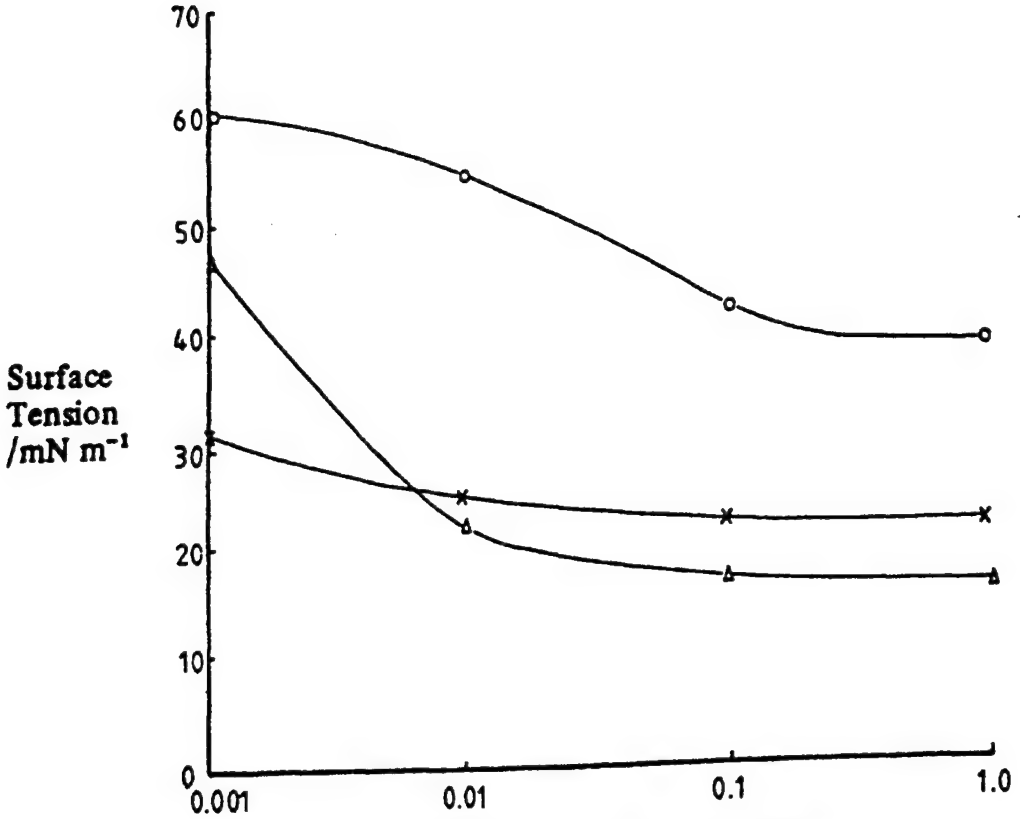
Perfluorinated Carboxybetaïne in aqueous solution



Perfluorinated carboxybetain in aqueous solution

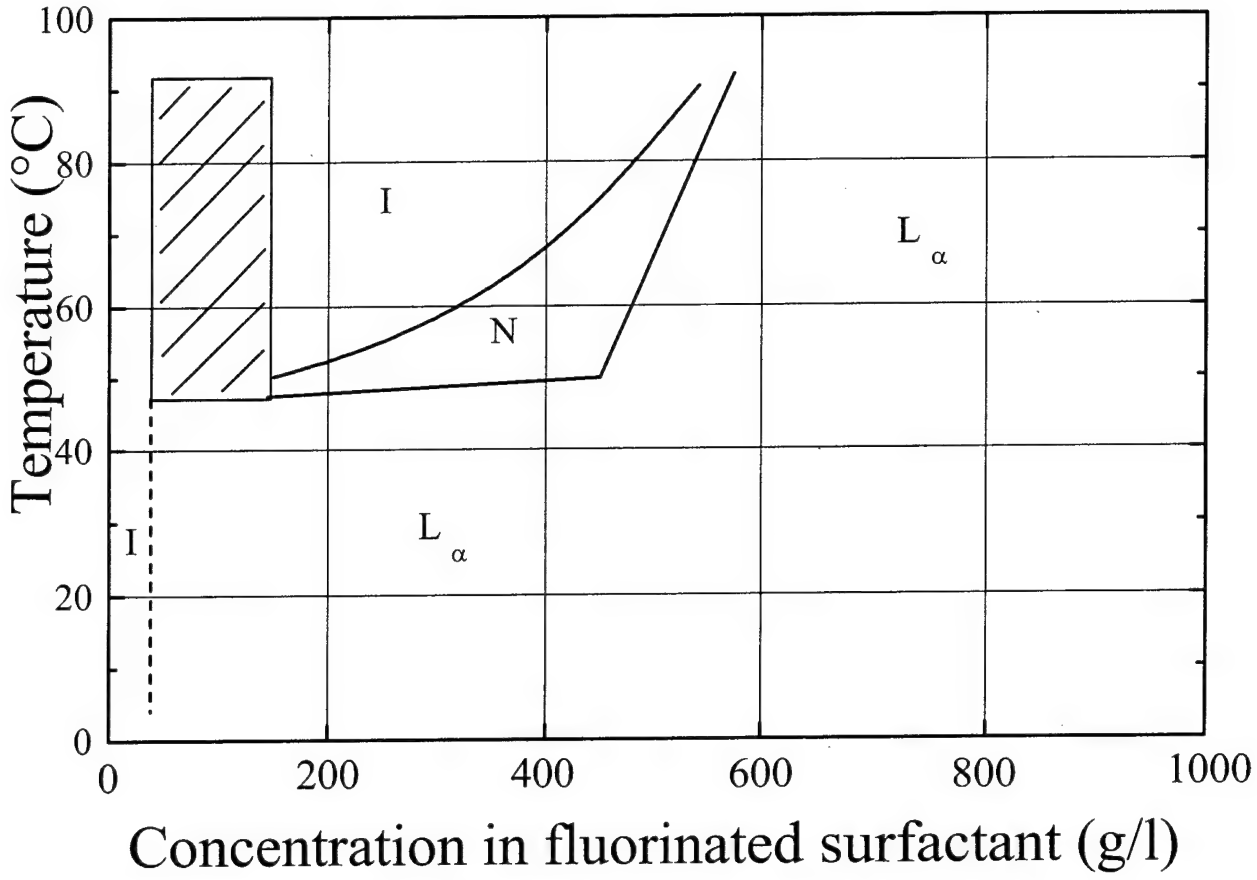


Fluorinated part structure: effect on the surface tension in water



– Surface tension Curves for: o Sodium lauryl sulphate; × Anionic based on branched-chain fluorochemical; ∆ Anionic based on straight-chain fluorochemical.

Perfluorinated carboxybetain in aqueous solution



USE OF AQUEOUS FOAM FOR FIRE FIGHTING

(SOLVENT FIRE)

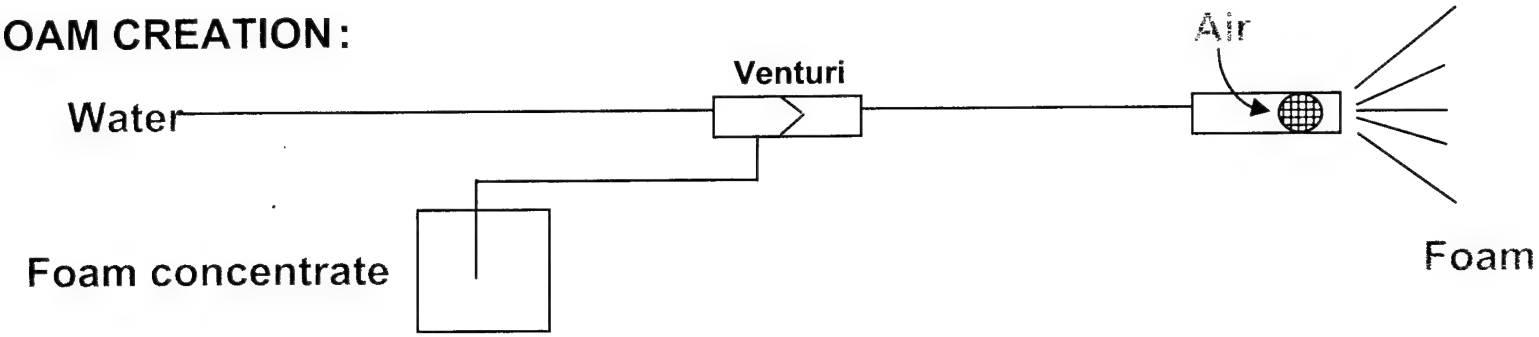
FOAM used to :

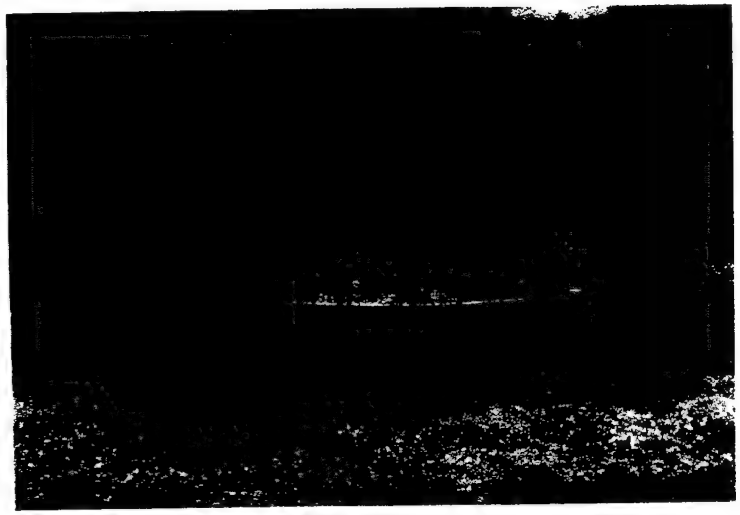
- **Stop the vapor emission**
- **Prevent flames from heating the solvent**

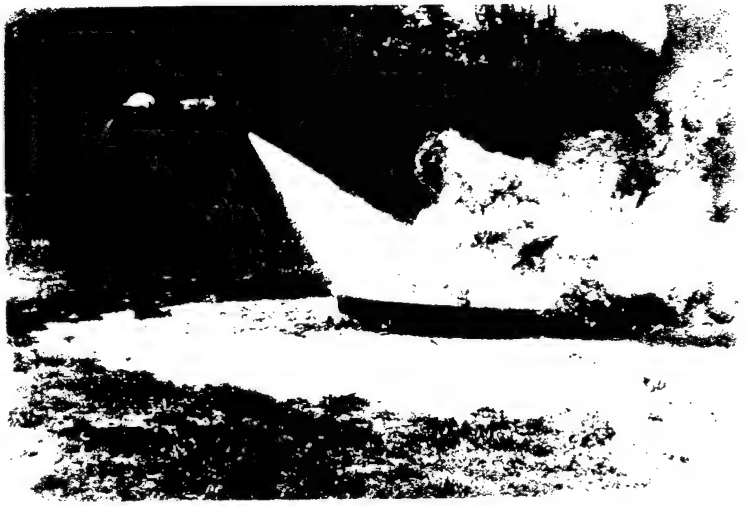
REQUIRED PROPERTIES:

- **Thermal stability as high as possible**
- **Positive spreading coefficient on the solvent**

FOAM CREATION :



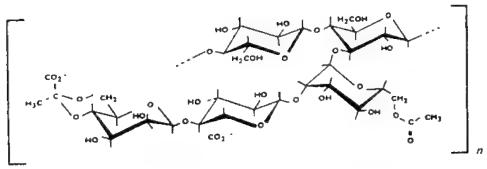




Composition of a foam concentrate

Hydrocarbon surfactant or protein	→	Foam formation
FLUORINATED SURFACTANT	→	Foam formation Spreading coefficient Thermal stability
Butylcarbytol	→	Foam stabilizer cosolvent for surfactants
1,2 propane diol	→	Protection against freezing
Polysaccharide	→	Gel formation at the solvent surface

$Mw \approx 2,5.10^6$



Conditions for a water film formation at the hydrocarbon surface

→ Spreading coefficient (SC) > 0

Hydrocarbon surface tension

Diluted foam concentrate surface tension

Interfacial tension between diluted foam concentrate and hydrocarbon

$$+3.5 = 25.3 - (15.8 + 6)$$

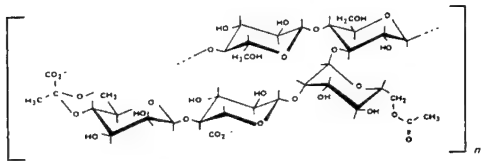
Use of fluorinated surfactants in order to lower the surface tension of the diluted foam concentrate

Use of hydrocarbon surfactants in order to lower interfacial tension between diluted foam concentrate and hydrocarbon

Composition of a foam concentrate

Hydrocarbon surfactant or protein	→	Foam formation
FLUORINATED SURFACTANT	→	Foam formation Spreading coefficient Thermal stability
Butylcarbytol	→	Foam stabilizer cosolvent for surfactants
1,2 propane diol	→	Protection against freezing
Polysaccharide	→	Gel formation at the solvent surface

$Mw \approx 2,5.10^6$

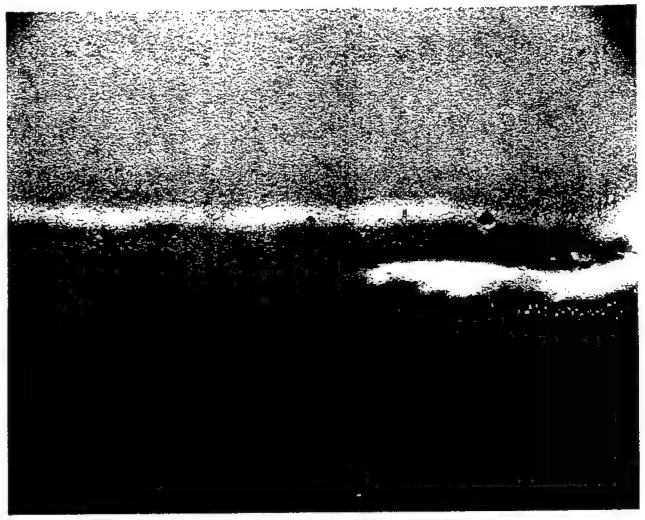


FORAFAC 1210 (Fluorinated water soluble telomer) in a proteinic foam concentrate

6% foam concentrate

F 1157 : 4%

+ Protéine



6% foam concentrate

F 1157 : 4%

+ Protéine

+ F1210

"Molécules amphipathiques perfluorées sur la base d'aminoacides ou d'oligopeptides"

Claude SELVE , Christine GERARDIN ,

Ludwig RODEHÜSER , Bernard HENRY

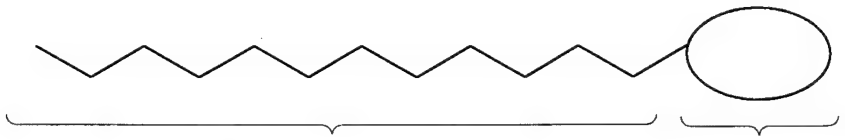
Université Henri Poincaré - Nancy I

Laboratoire de Chimie Physique Organique et Colloïdale.

UMR 7565 CNRS – UHP

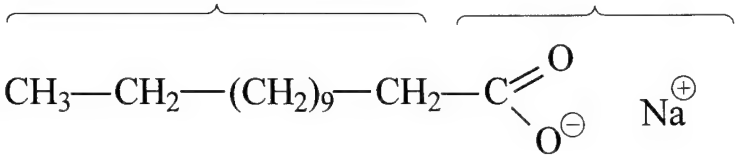
VANDOEUVRE les NANCY (France)

Structure bimodulaire d 'un surfactif

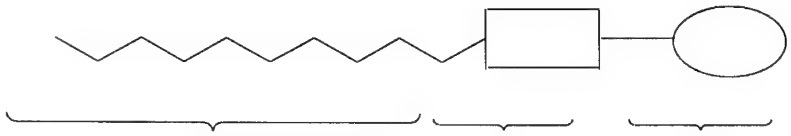


Hydrophobicity **Hydrophily**

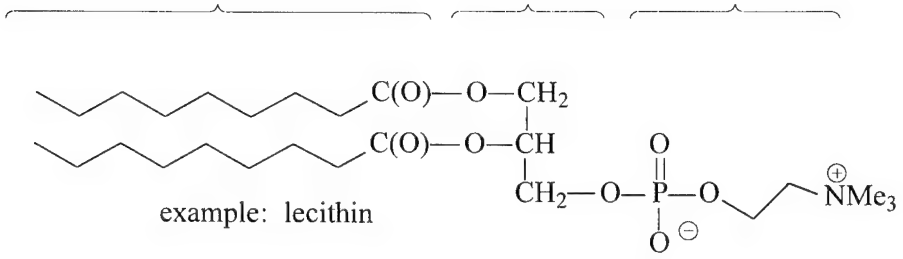
example : soap



Structure trimodulaire d 'un surfactif

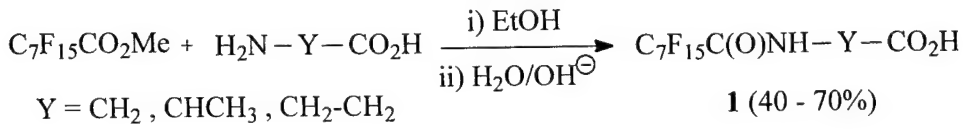


HYDROPHOBIC MODULUS HYDROPHILIC MODULUS

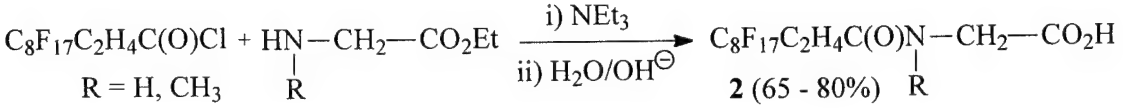


example: lecithin

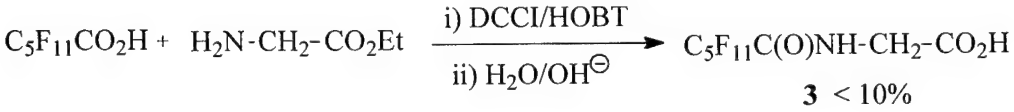
PerfluoroAlkyl-Acyl-aminoacids type 1



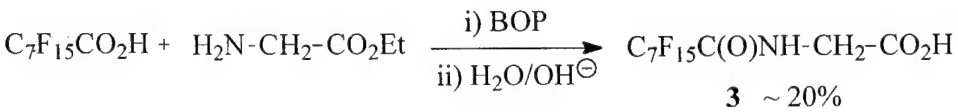
PerfluoroAlkyl-Acyl-aminoacides type 2



PerfluoroAlkyl-Acyl-aminoacides type 3



Autres synthèses de PerfluoroAlkyl-Acyl-aminoacides type 3

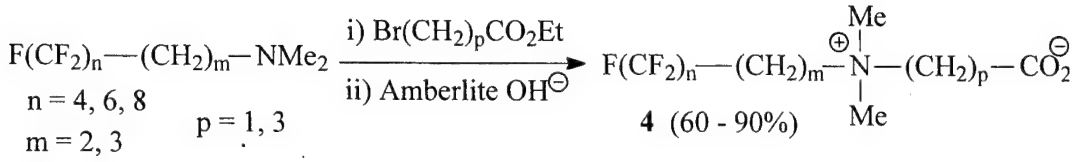


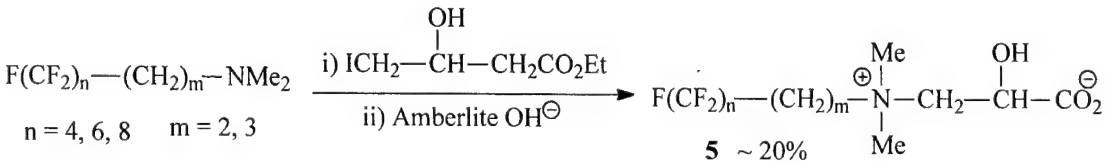
Produits très peu solubles dans l'eau ($<10^{-6}$)
Solubilité augmente aux pH élevés

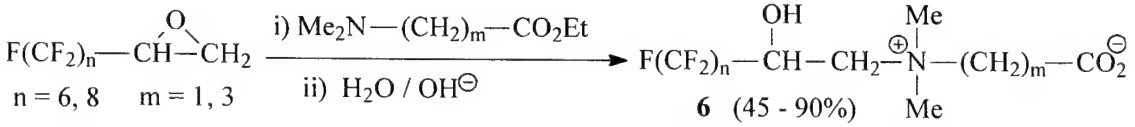
Références :

Kimura et al. : Yakagaku 1984
Blaignon; Riess : Thèse U. Nice (1987)
Gariser ; Selve : Thèse U. Nancy (1982)
König et al. : Chem. Ber. (1970)

PerfluoroAlkyl-Acyl-aminoacides type 4, 5 et 6



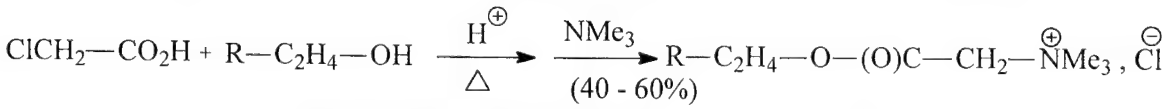




Produits permettant d'obtenir des vésicules et des agrégats globulaires

Murakami et al. : J. Am. Oil Chem. Soc. (1982) et J. Am. Chem. Soc. (1985).
Riess et al. : N. J. Chem. (1994) et Eur. J. Med Chem. (1992).

PerfluoroAlkyl-ester d'aminoacides type 7 et 8

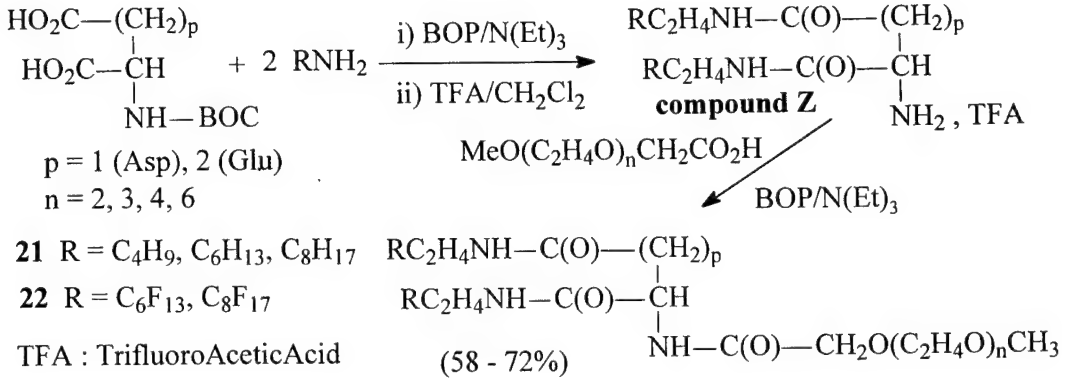


7 R = $C_{10}H_{21}$, $C_{12}H_{25}$, $C_{14}H_{29}$ **8** R = C_6F_{13} , C_8F_{17}

Bien solubles dans l'eau mais les dérivés perfluorés s'hydrolysent assez rapidement

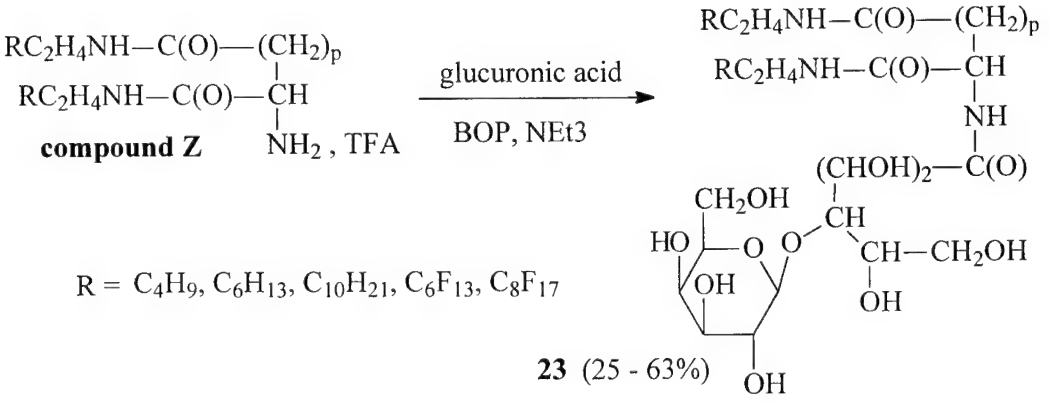
Riess et al. : N. J. Chem. (1994) et Eur. J. Med Chem. (1992).

Synthèses de diamides 21, 22, 23



Dérivés assez peu solubles dans l'eau

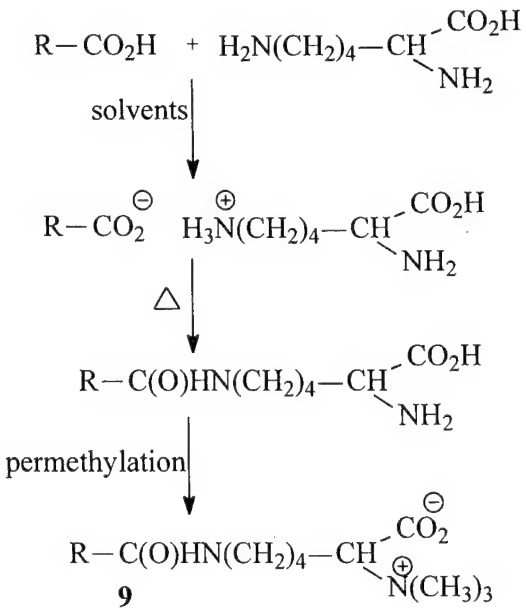
Allouch, Selve et al. : J. Am. Oil Chem. Soc. (1996)



Très bonne activité de surface, présentent une concentration critique

Allouch, Selve et al. : J. Comp. Esp. Dét. (1994)

Synthèses de composés Zwiterioniques par quaternisation de N-ε-Acyllysines 9 :



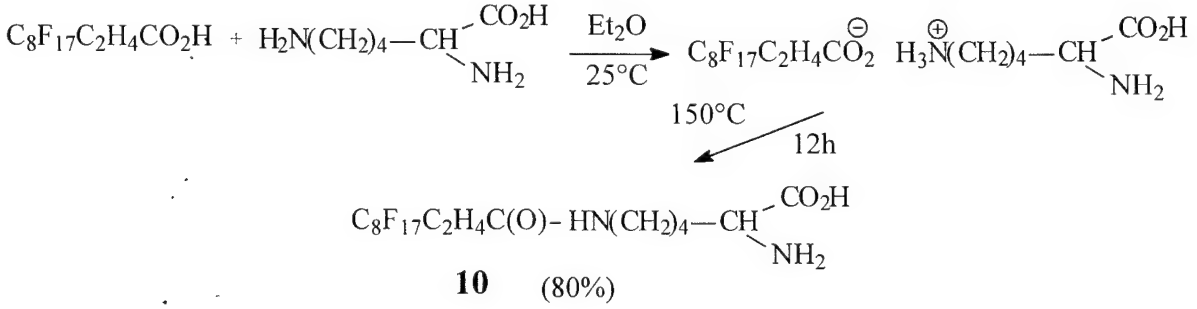
9

good surface agent with $R = H_3C(CH_2)_n$ [n = 10, 14]

Yokota *et al.* : J. Am. Oil Chem. Soc. (1985)

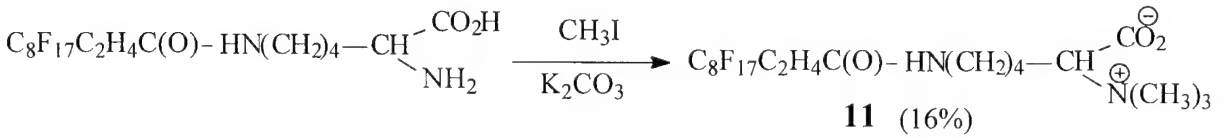
Sur ce principe :

Synthèses de N-ε-Perfluoroalkyl-Acyllysines 10 :



10 (80%)

Quaternisation de N-ε-Perfluoroalkyl-Acyllysines :

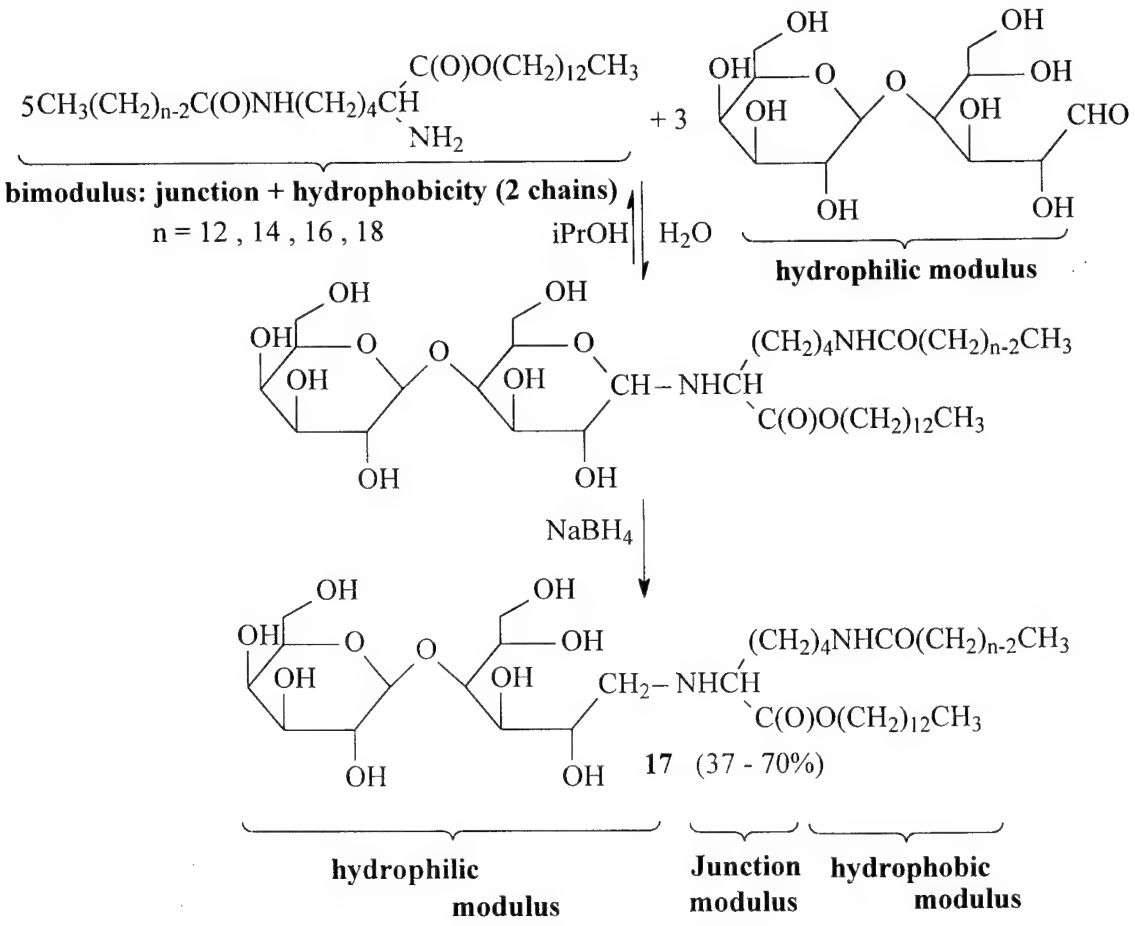


11 (16%)

Assez solubles dans l'eau ; Présentent une Concentration critique [courbe γ=f(logC)]
Blaignon; Riess : Thèse U. Nice (1987)]

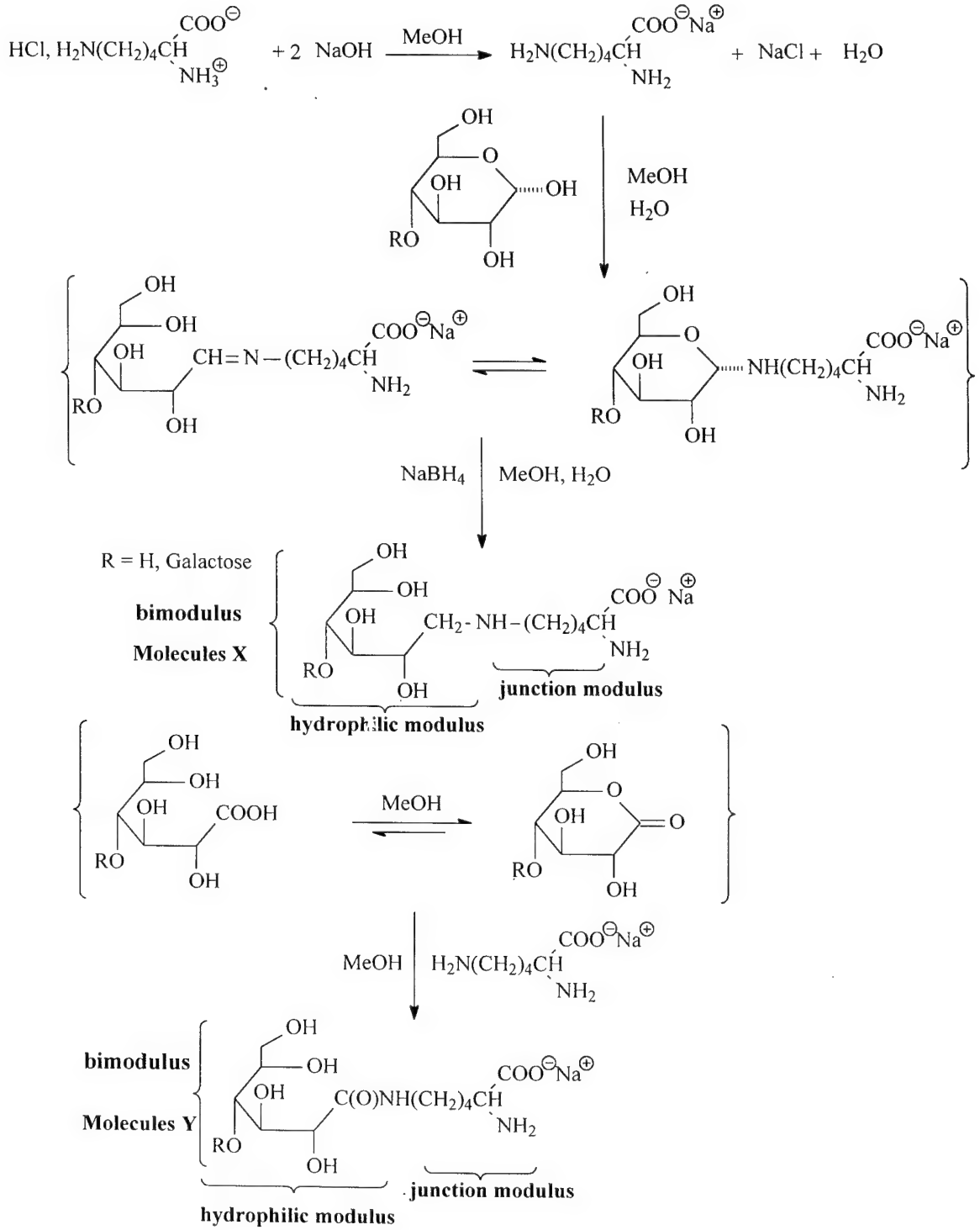
Exemple de synthèse trimodulaire

Synthèse de ε-alcanoylamido-α-lactylamino-lysine 17

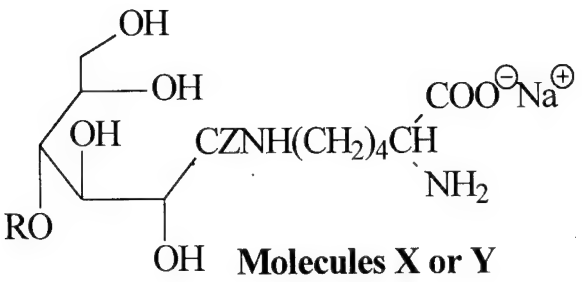


Autre stratégie

Préparation de composés hydrophiles bimodulaires "Lys-Sugar" : X et Y



Synthèse de surfactifs monocaténaires type 18



Molecules X or Y

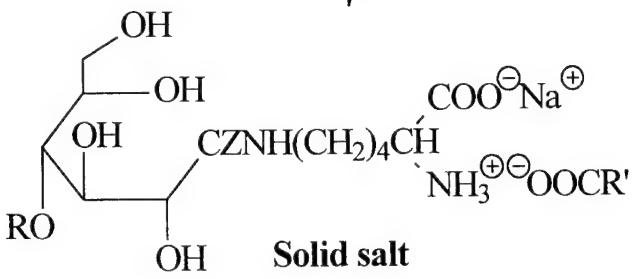
R'COOH

fatty acid

R = H, Galactose

Z = H_2, O

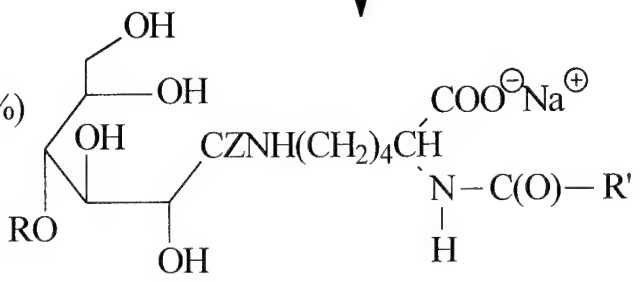
H_2O ⇅ MeOH



Solid salt

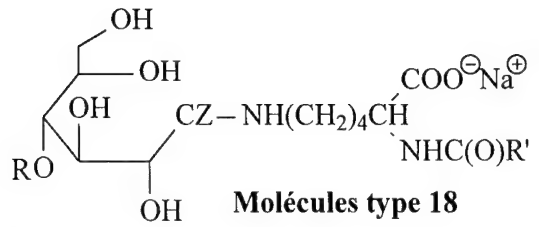
Toluene or heptane ; △, 24 - 36h

18 (50 - 97%)



R' = $C_{10}H_{21}$, $C_{12}H_{25}$, $C_{16}H_{33}$, $C_{18}H_{37}$, $C_6F_{13}CH_2$, $C_8F_{17}CH_2$

Synthèse de surfactifs bicaténaires type 19



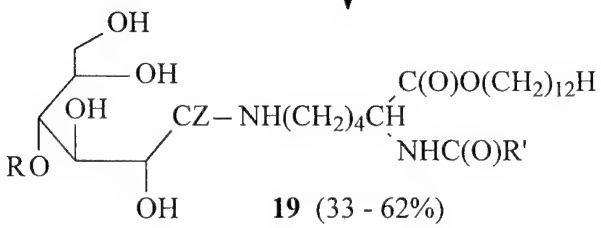
Molécules type 18

R = H, Galactose

Z = H_2, O

Toluène
△, H_2SO_4

$H(CH_2)_{12}OH$



19 (33 - 62%)

R' = $C_{10}H_{21}$, $C_{12}H_{25}$, $C_{16}H_{33}$, $C_{18}H_{37}$, $C_6F_{13}CH_2$, $C_8F_{17}CH_2$

Surfactants bicaténaires non ioniques

Présentent une CMC (γ= f(logC)

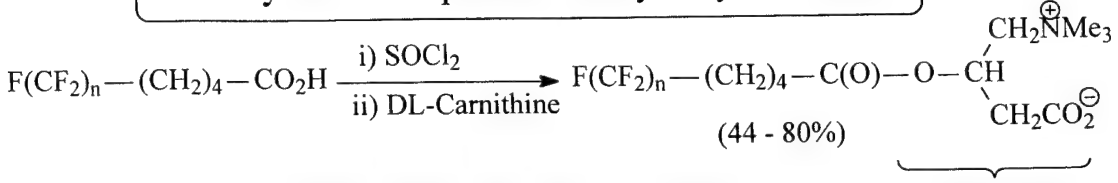
Forment des phases Lα et des vésicules (sonication ou extrusion)

Les molécules à chaînes pefluorées sont peu solubles dans l'eau ($<10^{-6}$)

Les molécules mixtes (fluorées-hydrogénées) sont en cours d'études.

Selve et al. : unpublished results

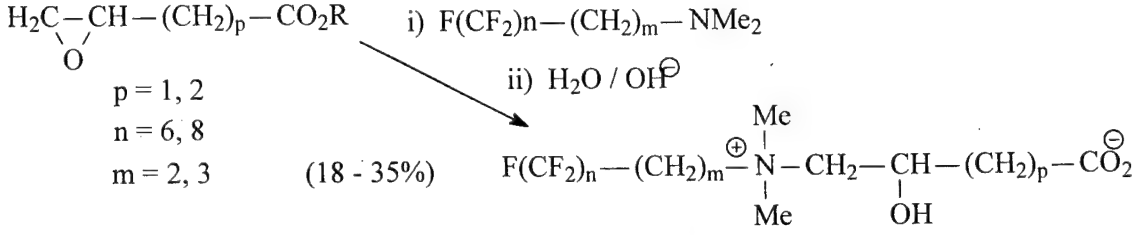
Synthèse de perfluoroalkyl-acyl-carnitine



Très bonnes activités de surface

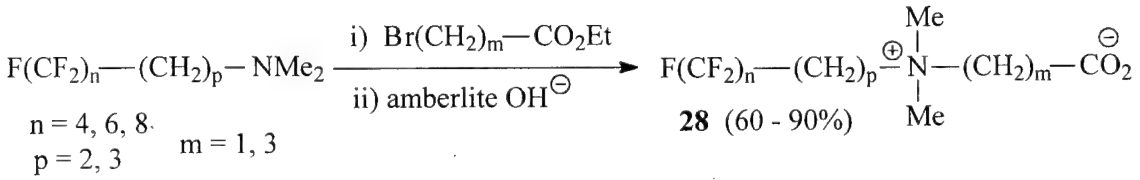
Riess et al. : Eur. J. Med. Chem. (1991)

Synthèse de N-perfluoroalkyl-carnitine



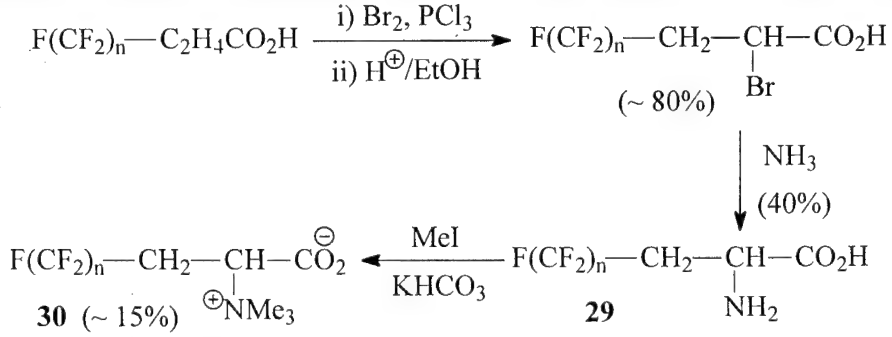
Riess et al. : New. J. Chem. (1994)

Synthèse de la bétaïne 28



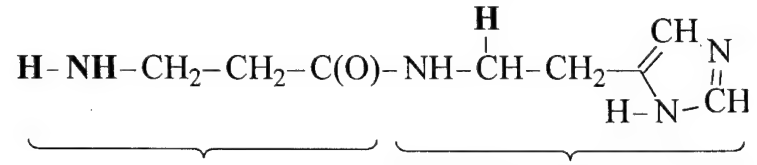
Riess et al. : Eur. J. Med. Chem. (1992)

Synthèse d'α-perfluoroalkyl-Gly 29 et la bétaïne correspondante 30



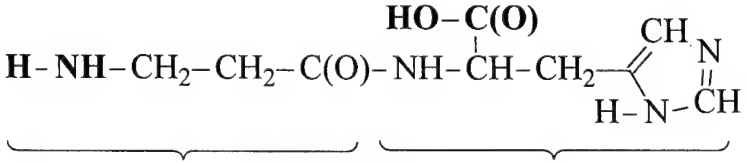
Toutes ces molécules présentent de bonnes activités de surface, elles sont non hémolytiques pour les globules rouges et leur cytotoxicité est très faible.
Riess et al. : Int. Chem. Cong. Pacific Soc. org. (1989)

Carcinine :



β-Alanine **Histamine**

Carnosine :



β-Alanine **Histidine**

Ces molécules sont présentes dans les tissus animaux et humains, en particulier au niveau musculaire, leurs activités biologiques ne sont pas complètement cernées

Il a été montré que leur rôle principal serait une protection contre les effets pernicieux des peroxydes : ***rôle antioxydant***

Celui-ci semblant être lié à leur propriétés complexantes des cations métalliques tels que Cu, Zn, Co…
Le complexe serait le véritable acteur dans l'acte antioxydant

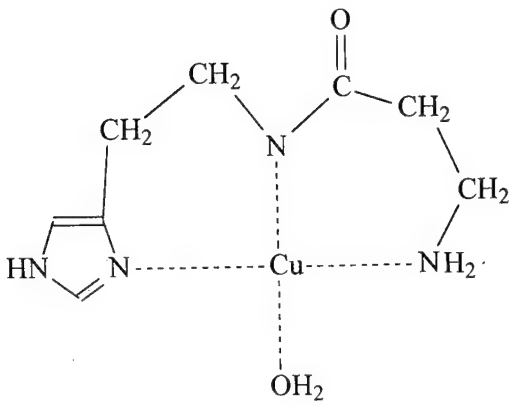
Utilisation comme modules hydrophiles dans des tensioactifs

Donc recherche de molécules présentant des :

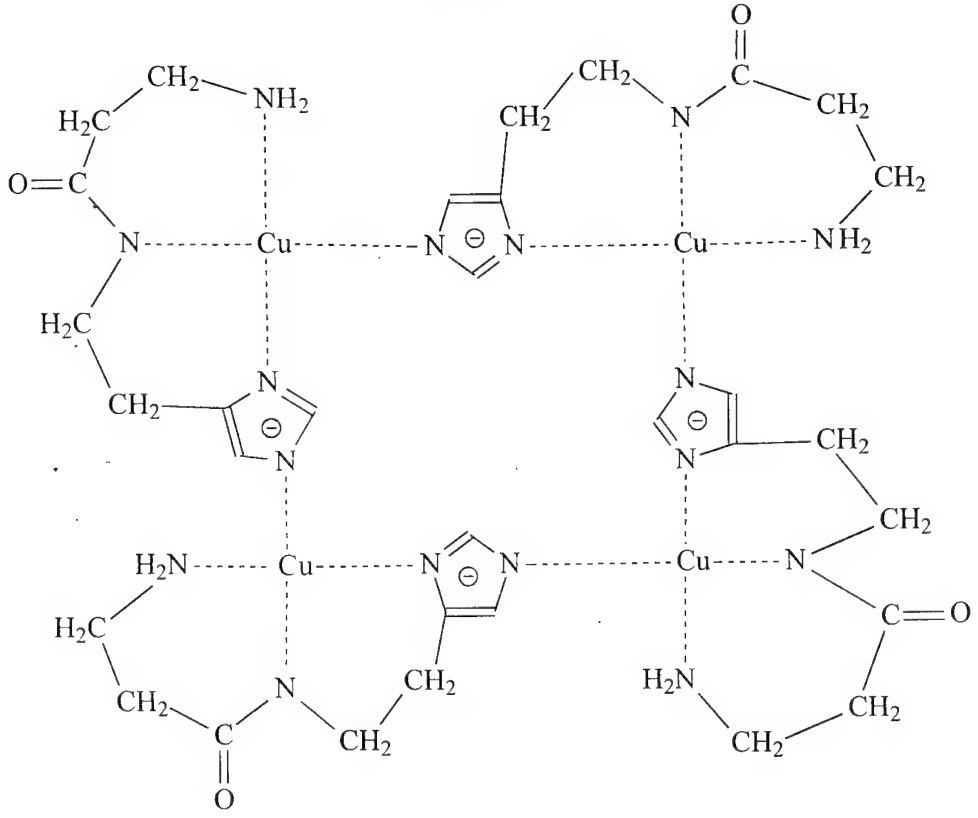
- ***Propriétés de surfaces***
- ***Propriétés complexantes des cations***
- ***Propriétés antioxydantes***

Structures schématiques de quelques complexes formés dans le système Cu(II)-carcinine

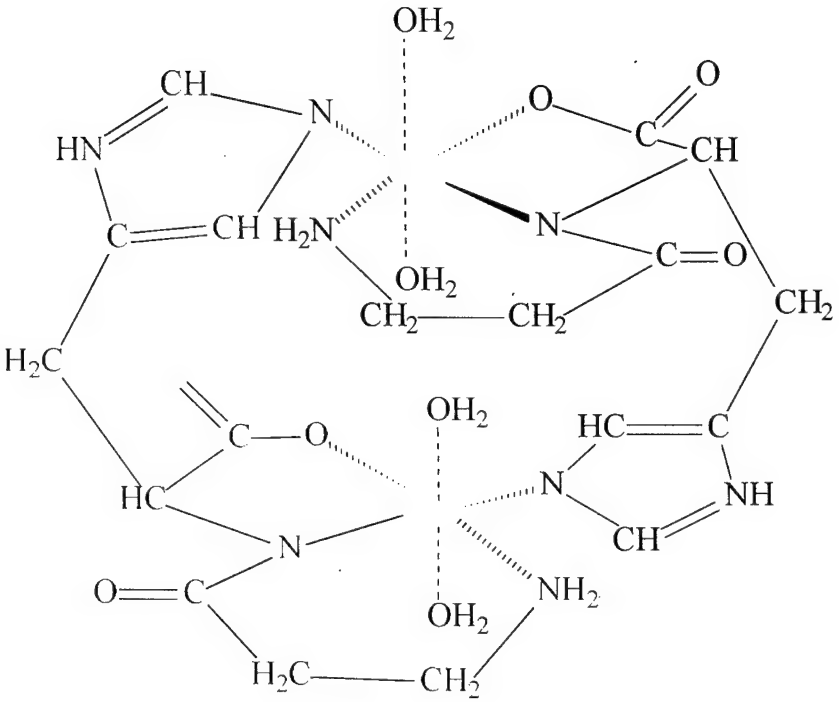
$CuLH_{-1}$



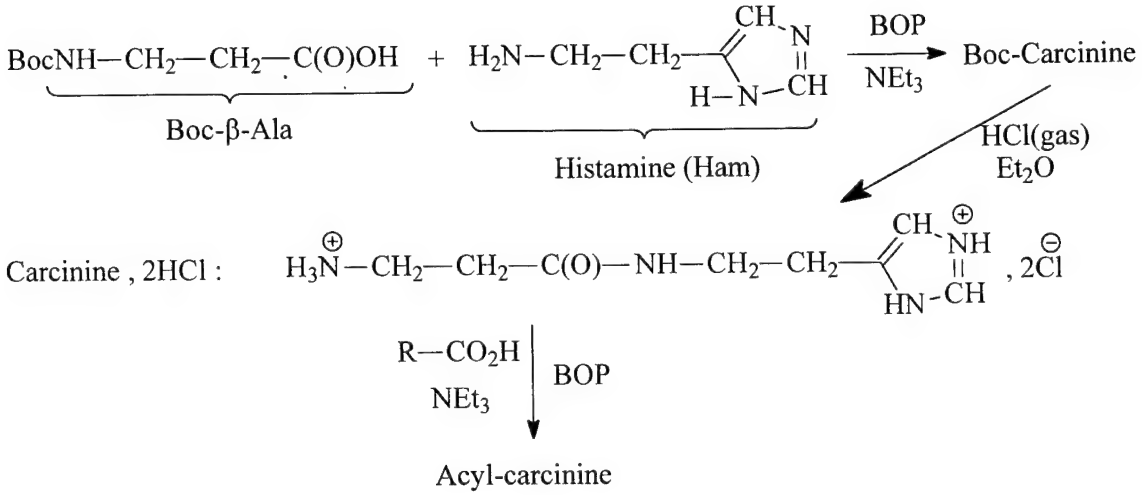
$Cu_4L_4H_{-1}$

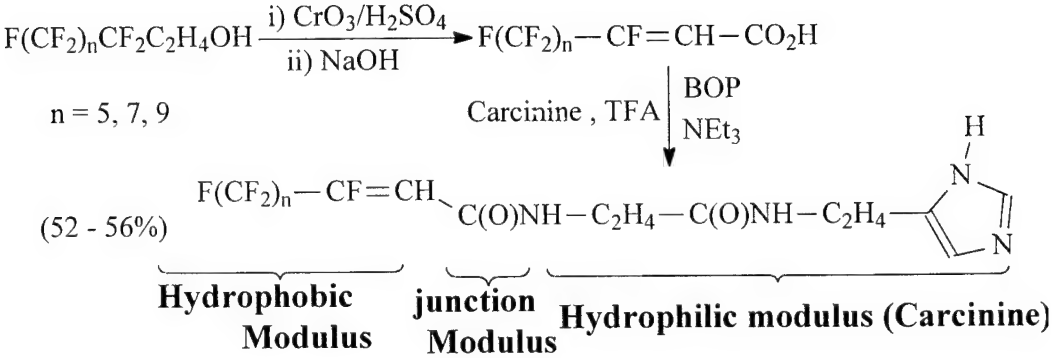


Structure schématique d 'un complexe formé
dans le système Cu(II)-carnosine

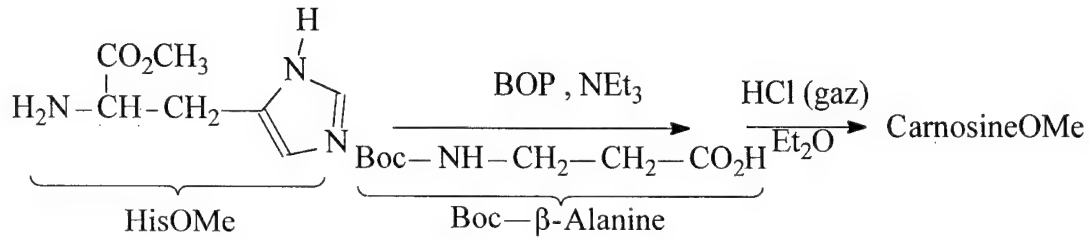


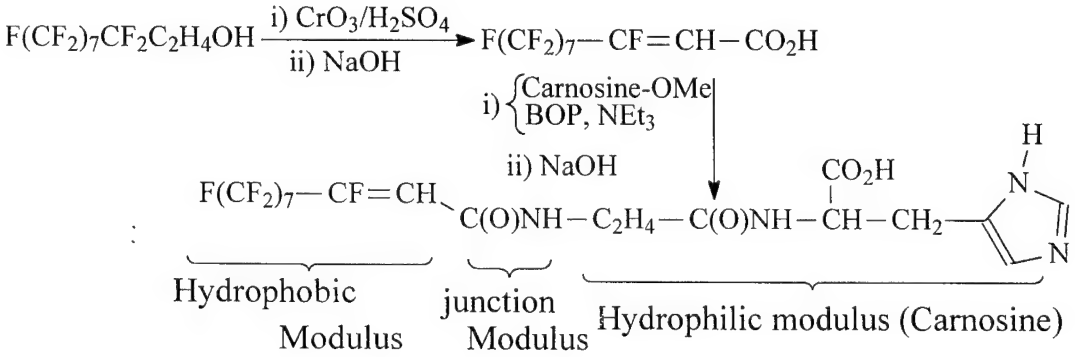
Synthèses de surfactifs acyl-carcinine



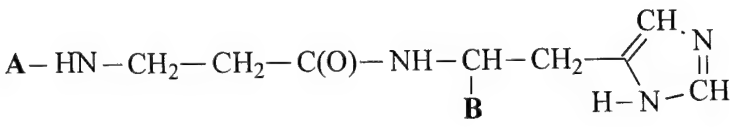


Synthèses d'alkylamido-carnosines amphipathiques



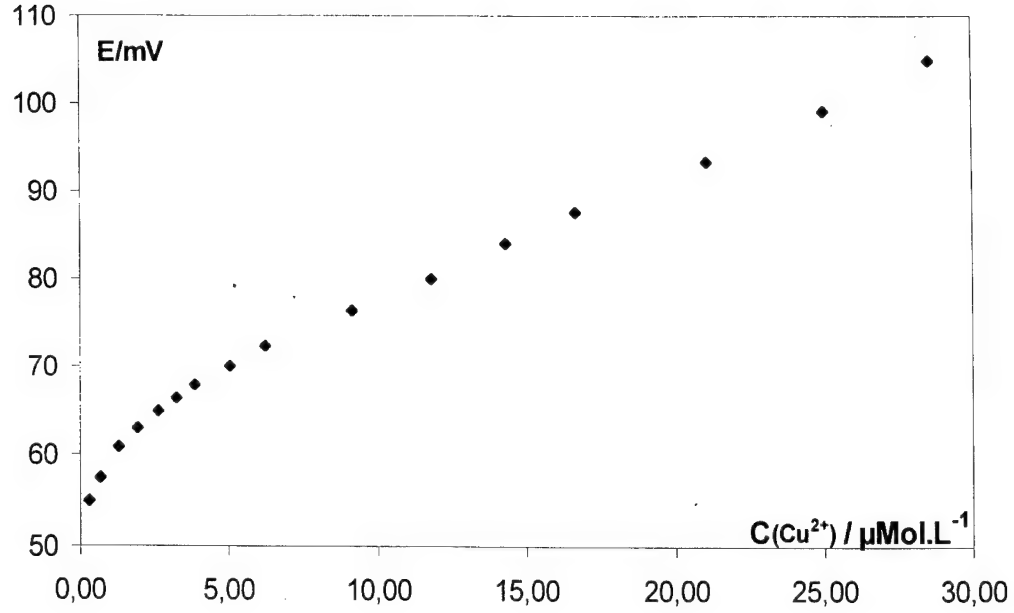


Quelques résultats : Acyl-carcinines et carnosines -alkylaminées

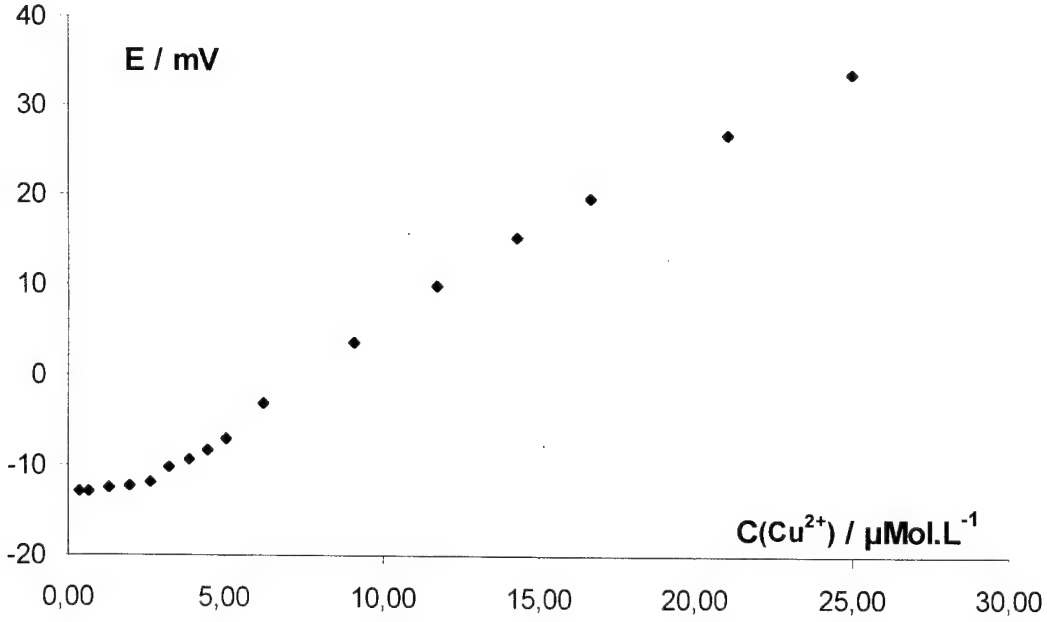


A	B	Yields %	CMC $M.L^{-1}$ 10^4
$C_5F_{11}CF=CH-C(O)$	H	61	56
$C_7F_{15}CF=CH-C(O)$	H	74	7.5
$H(CH_2)_9-C(O)$	H	65	77
$H(CH_2)_{11}-C(O)$	H	73	6.8
H	$C(O)-NH-(CH_2)_8H$	84	-
H	$C(O)-NH-(CH_2)_{10}H$	80	95
H	$C(O)-NH-(CH_2)_{14}H$	81	-
H	$C(O)-NH-C_2H_4C_6F_{13}$	67	72
H	$C(O)-NH-C_2H_4C_8F_{17}$	68	0.92

A)

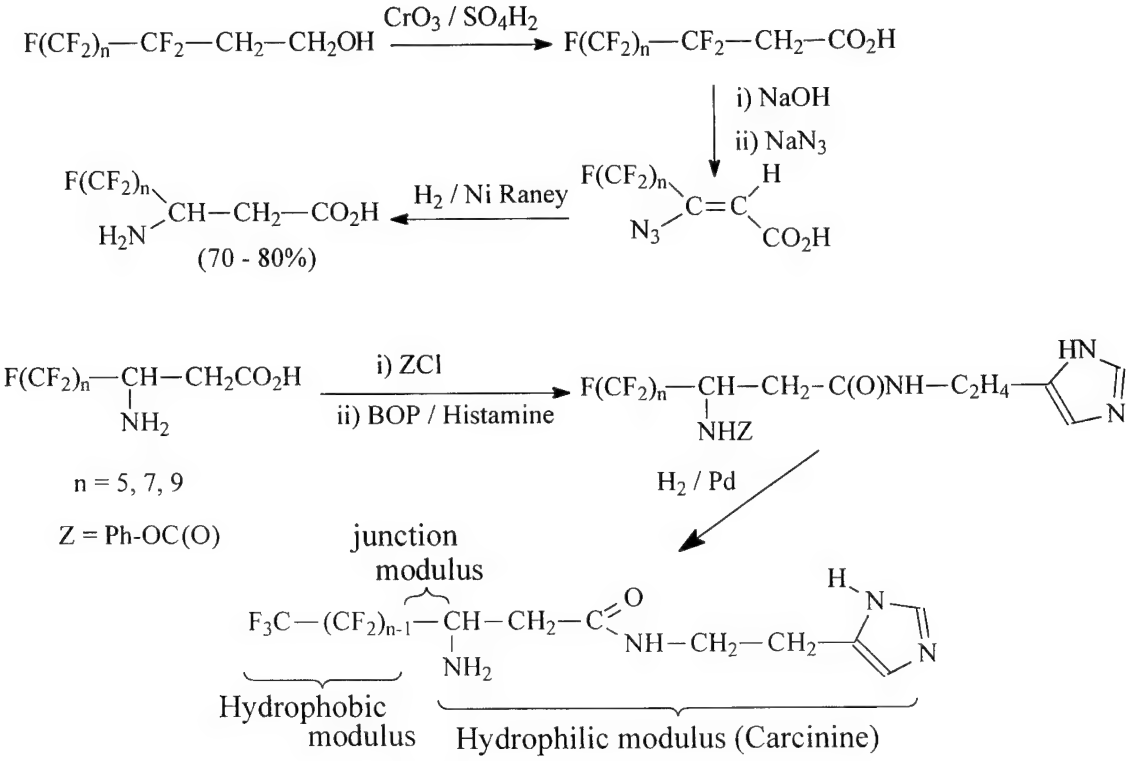


B)



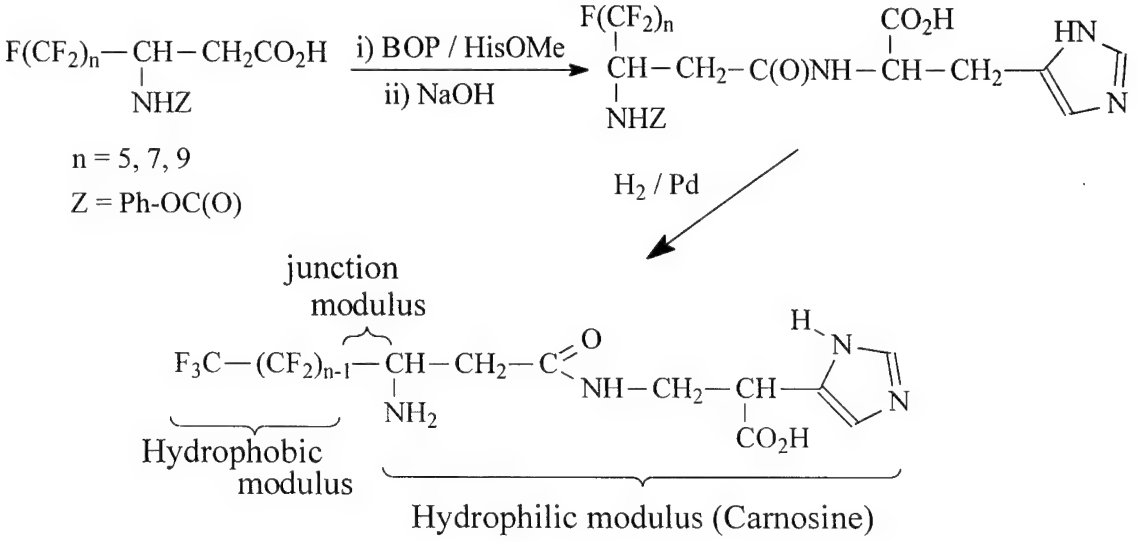
Ion Selective Electrode measurements of copper(II) ion activity in the presence of $H(CH_2)_9C(O)$-carcinine (A), and carnosine-$NH(CH_2)_{10}H$ (B)as a function of total copper concentration. [T = 25°C, pH = 6.]

Synthèses de β-perfluoroalkyl-β-Alanine et utilisations pour la synthèse de D, L-perfluoroalkyl-β-Alanyl-Histamine



(70 - 80%) perfluoroalkyl-carcinine

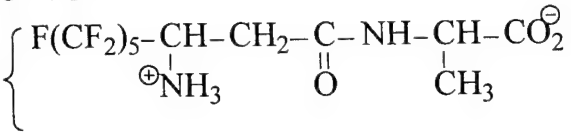
Synthèses de D, L-perfluoroalkyl-β-Alanyl-Histidine



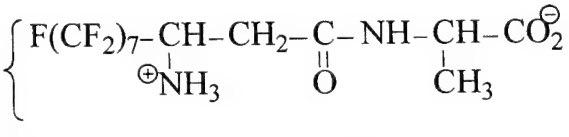
(50 - 60%) perfluoroalkyl-carnosine

courbes $\gamma = f(\log C)$ pour :

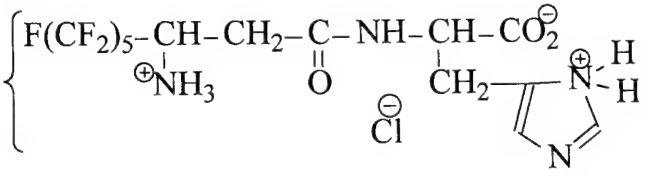
AA5H

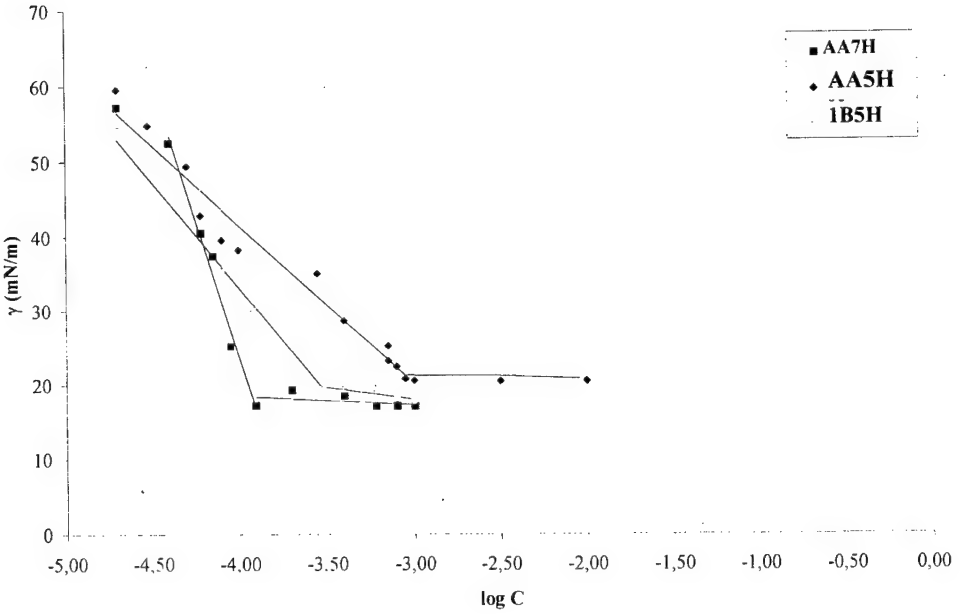


AA7H

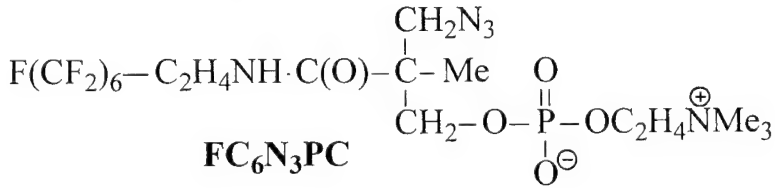


1B5H

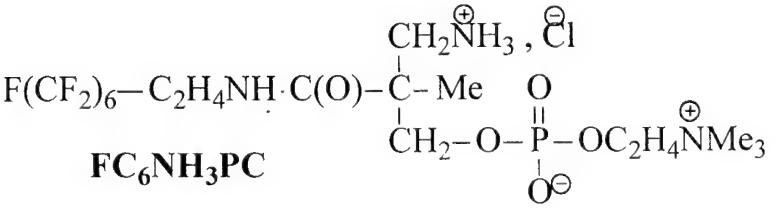




Structure of lyso-lecithin analogues (Papadopoulos1996)



FC_6N_3PC



FC_6NH_3PC

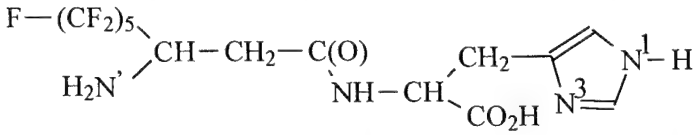
Minimal surface tension (γ_{CMC}) and critical micelle concentration (CMC) for aqueous solutions of derivatives **AA5**, **AA7,** and **1B5-HCl** as well as of analogous compounds reported in the literature

Compound	γ_{CMC} ± 1 mN/m	**CMC.10^4** M/L	**Factor**	**Ref.**
1B5-HCl : **RF5-Carnosine**, HCl	19	29,5	3	This work
AAC5 C5Ala-Ala	19	10		
AAC7 C7Ala-Ala	16	1,2	10	
$F(CF_2)_6$-CH_2-$(OC_2H_4)_4$-OH	18	1,17	3	[1]
$F(CF_2)_7$-CH_2-$(OC_2H_4)_4$-OH	17	0,41		
$F(CF_2)_6$-CH_2-$(OC_2H_4)_4$-OCH_3	18	1,15	3	
$F(CF_2)_7$-CH_2-$(OC_2H_4)_4$-OCH_3	17	0,39		
$F(CF_2)_6$-CH_2-C(O)-Gly-Sar-GlyNH_2	17	15	10	[2]
$F(CF_2)_8$-CH_2-C(O)-Gly-Sar-GlyNH_2	16	1,3		
FC_6N_3PC (Papadopoulos)	23	7,6	5	[3]
FC_6NH_3PC (Papadopoulos)	25	38		

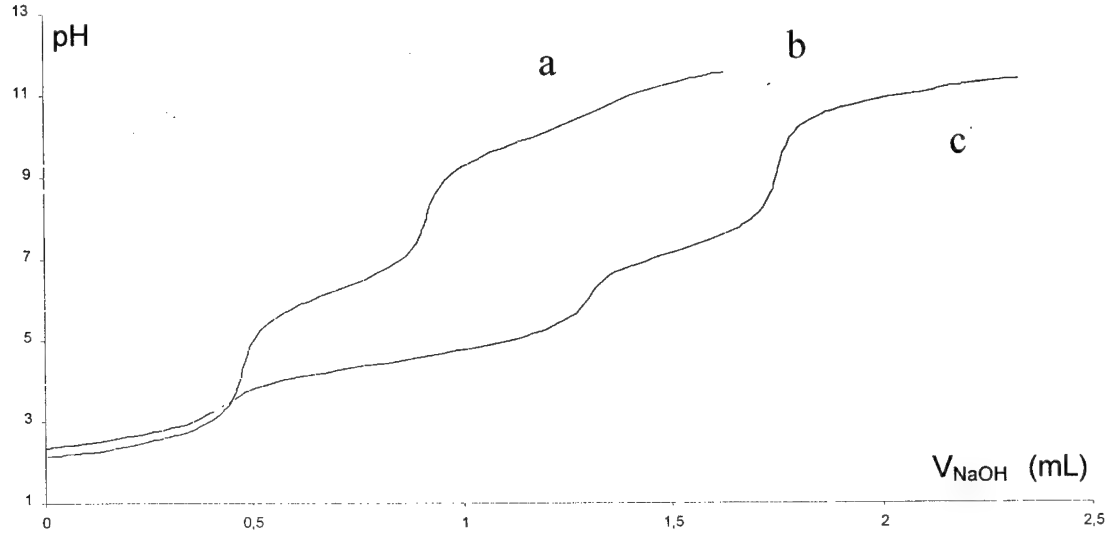
1 - S. Achilefu, PhD Thesis, University Henri Poincare Nancy I (1991).
2 - F. Hamdoune, C. Selve, L. Mansuy, M. Allouch, J. Chem. Res.., (1992).
3 - D. Papadopoulos, S. Auberger, C. Gérardin, J. Amos, M. Maugras, M.J. Stébé, C. Selve, New J. Chem., (1999)

The **pK-values and complexing properties** of compound **1B5** have been investigated by acid-base titrations and UV/vis spectroscopy.

. Structure of "C_5F_{11} – carnosine" 1B5, showing the numbering of imidazole nitrogen atoms



. Titration curves of the system Cu^{2+}-**1B5** with 0.1 molar NaOH starting from 5 mL of $8.9.10^{-3}$ molar **1B5** and (a) 0 mL, (b) 2 mL, and (c) 4.25 mL of $9.9.10^{-3}$ molar $Cu(ClO_4)_2$ solutions.



The pK-values of the different protonated sites of the free ligand have been extracted from the titration curves by using the PSEQUAD software developed by Zekany . They are listed in table (second column). For comparison those reported in previous literature for unsubstituted carnosine are also included in the table.

Table . pK-values for free 1B5 and literature values for carnosine.

	this work	Gajda [1]	Sovago [2]	Brookes [3]
pK_{COOH}	1.24	2.66	2.53	2.60
$pK_N{}^3$	6.11	6.77	6.84	6.83
$pK_{N'}$	9.81	9.38	9.30	9.46

1 - T. Gajda, PhD Thesis, University Henri Poincaré Nancy I (1994)

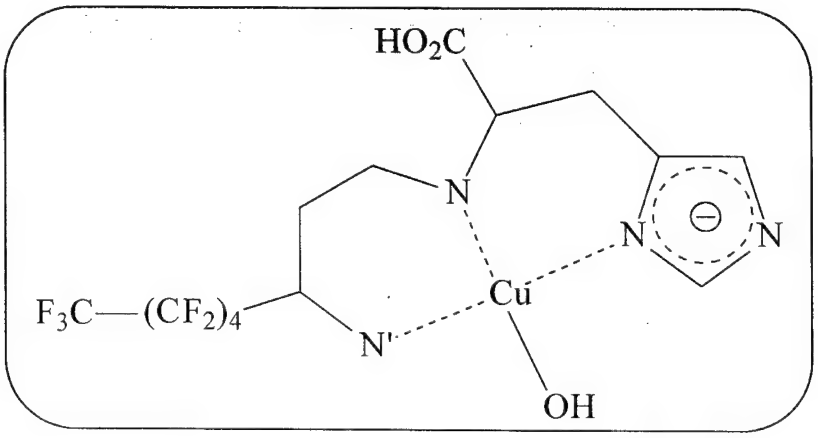
2 – I. Sovago et al., J. Chem. Soc. Dalton Trans. (1982).

3 – G. Brookes et al., J. Chem. Soc. Dalton Trans. (1975).

In spite of the electron-withdrawing character of the perfluoroalkyl chain, supposed to increase the acidity of the amino group in the α-position ($N'H_2$), a decrease in acidity is actually observed, whereas the other protonated sites become more acid as expected. This observation may be explained by local variations of the pK-values of the titrated functions when the molecules are engaged in micellar structures.

The results from the titration experiments combined with those of complementary UV/vis investigations are in agreement with a structure of the copper complex as schematically shown below.
At pH values above 7.5 the titration data show that three nitrogen binding sites are available for co-ordination to copper and the maximum in the electronic spectra of the copper ion, situated at $\lambda \sim 620$ nm suggests that three nitrogen atoms are engaged in the first co-ordination sphere of the metal ion.

. Schematic structure of the copper(II) - "RF5-carnosine" (**1B5**) complex.



CONCLUSIONS :

Since the ligand **1B5** binds efficiently to copper(II), similar types of complexes can be predicted for other divalent transition ions such as Ni^{2+} and Co^{2+}.

CONCLUSIONS :

Les Amphihiles perfluorés basés sur un aminoacide ou un peptide ont été très fortement travaillés et de très nombreuses structures ont été préparées:

Les synthèses utilisent toutes les méthodes de la chimie organique avec des résultats variables mais généralement corrects voire très bons

Les méthodologies mises au point se caractérisent de plus en plus par une forte recherche de **simplicité chimique** dans les mises en œuvre: on essaie en particulier d'éviter le plus possible le recours aux stratégies de "protections – déprotections".

Cette volonté de recherche de méthodes les plus directes possibles s'inscrit dans une démarches forte de retombées vers **les applications** potentielles des **amphiphiles fluorés**. Un de leur inconvénient majeur est leur "prix élevé" : une chimie simple et directe participe à en abaisser le coût et offre au chercheur une opportunité de rechercher des sélectivités sur les molécules polyfonctionnelles comme les aminoacides.

Les démarches basées sur des structures oligopeptidiques ou pseudopeptidiques sont également réalisées (Exemple : nos démarches avec les peptidoamines) pour obtenir des **dérivés présentant des propriétés physico-chimiques multiples et originales.**

Il est certain que l'ensemble de travaux de ce type enrichissent les connaissances chimiques, physico-chimiques avec des retombées biologiques et environnementales.

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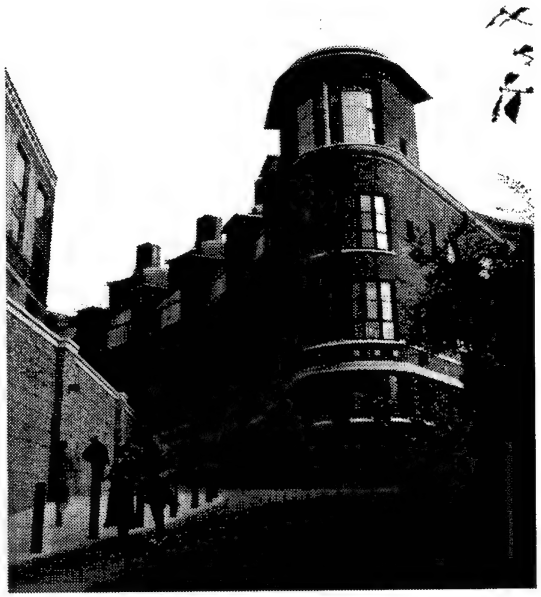
School of Chemistry

University of Bristol - UK



❶ introduction

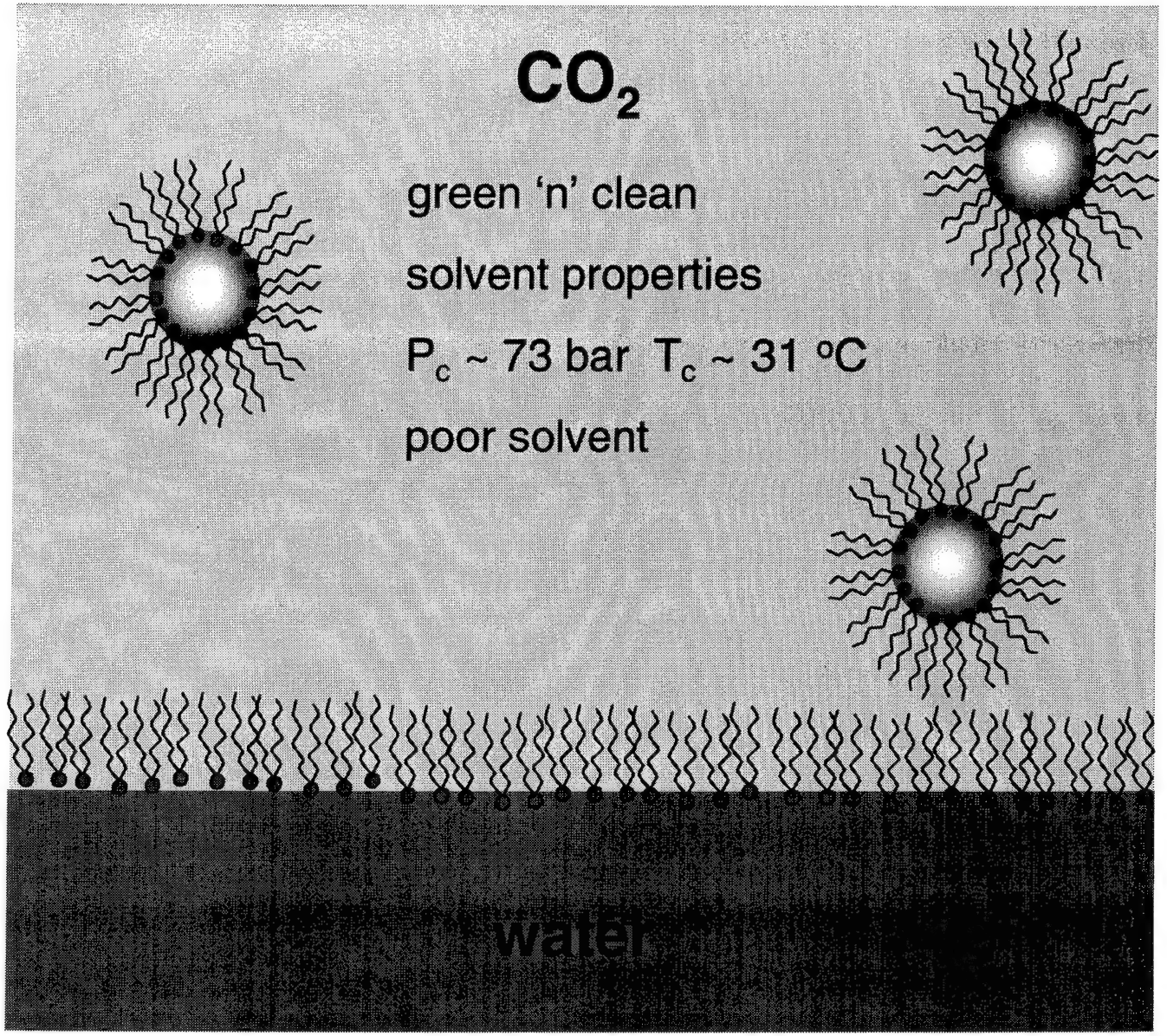
❷ surfactants

❸ aqueous phase behaviour

❹ water-in-CO_2 microemulsions

❺ conclusions

❶ introduction



❶ introduction

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The dry cleaning industry is under increasing scrutiny. Its primary cleaning solvent, perchloroethylene, has been identified as a ground water contaminant and a potential health concern.

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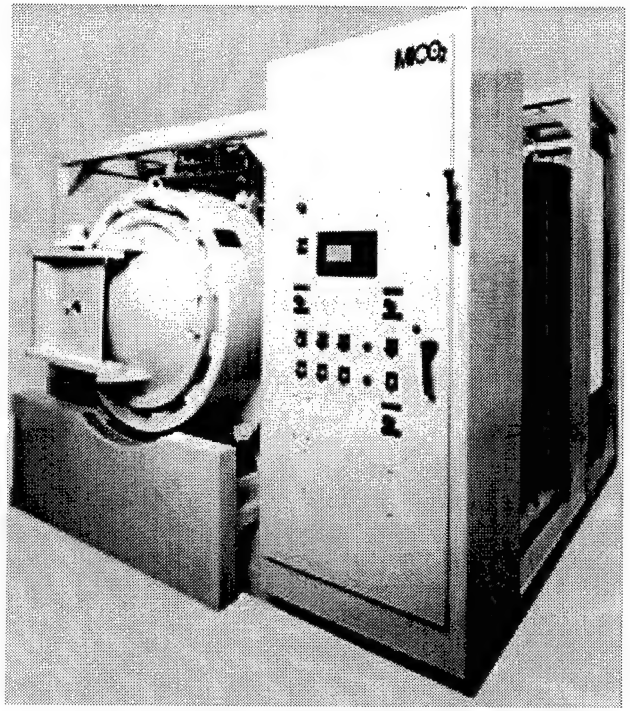
Carbon dioxide technology developed by Micell Technologies® solves the perchloroethylene and petroleum problems. It's environmentally friendly, requires no governmental paperwork or special taxes and it eliminates the need for hazardous waste removal

❶ introduction

www.micell.com



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SYSTEM

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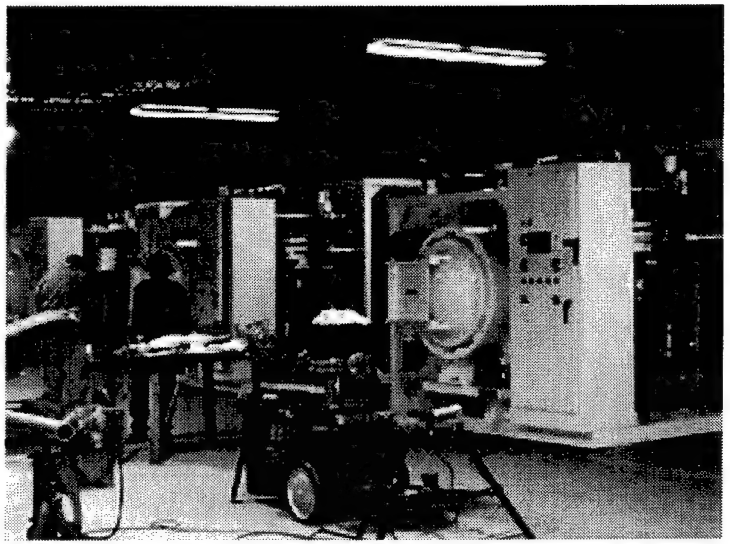

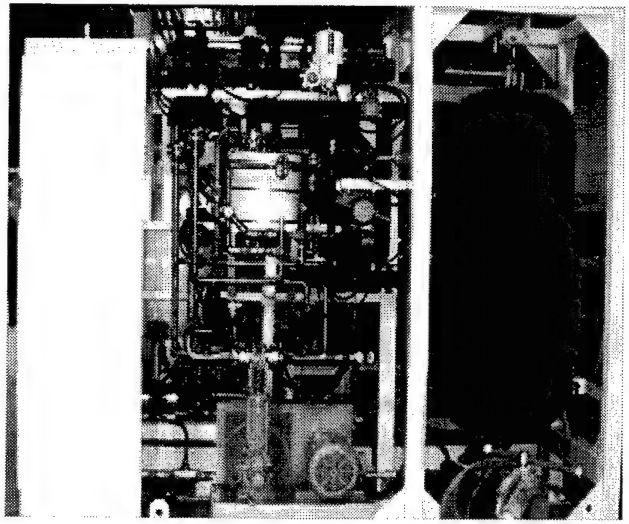

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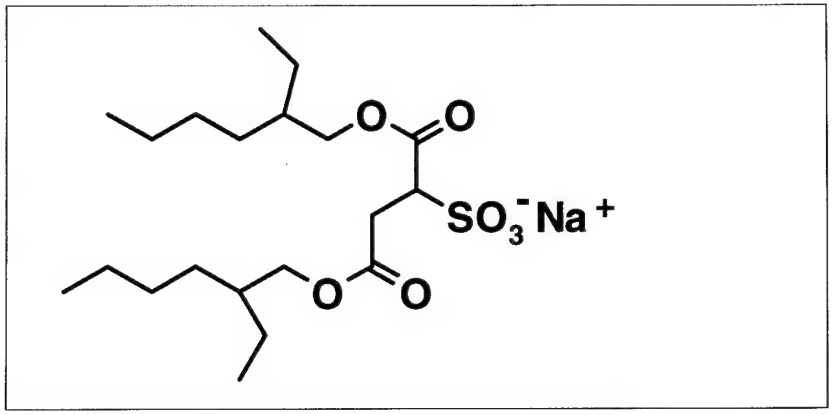
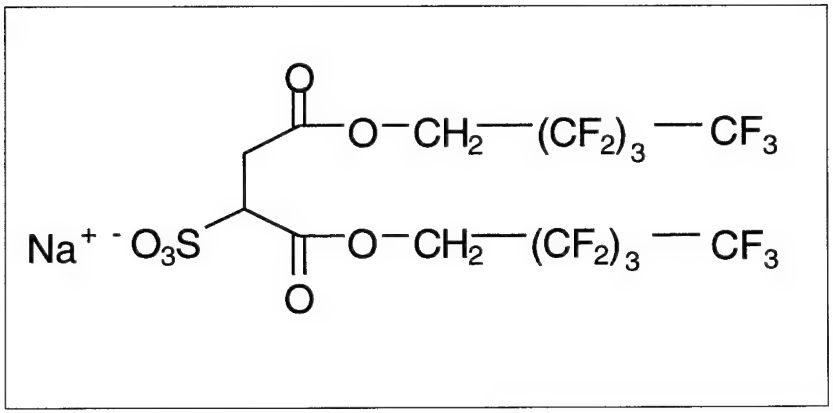
❷ surfactants



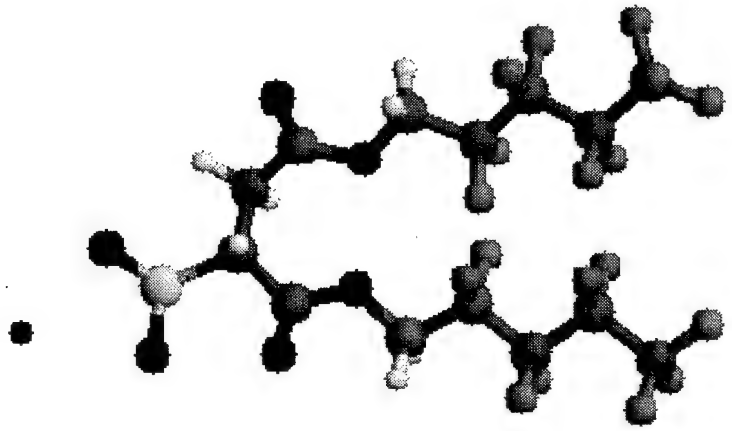
AOT

sodium bis (2-ethyl-1-hexyl) sulfosuccinate

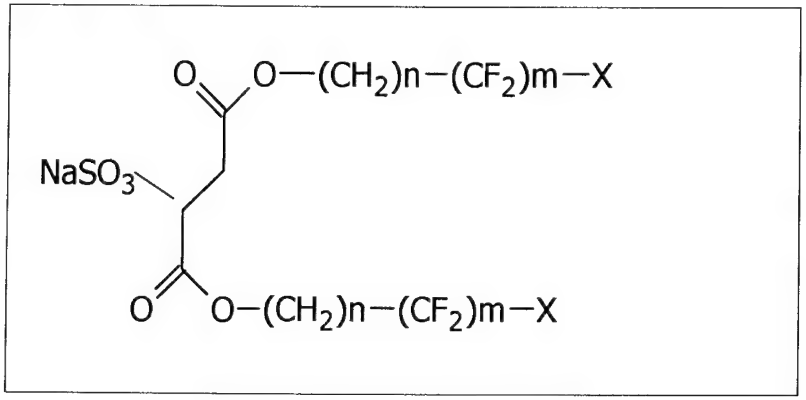


di-CF4

bis(1H,1H-nonafluoro-pentyl) sodium sulfosuccinate

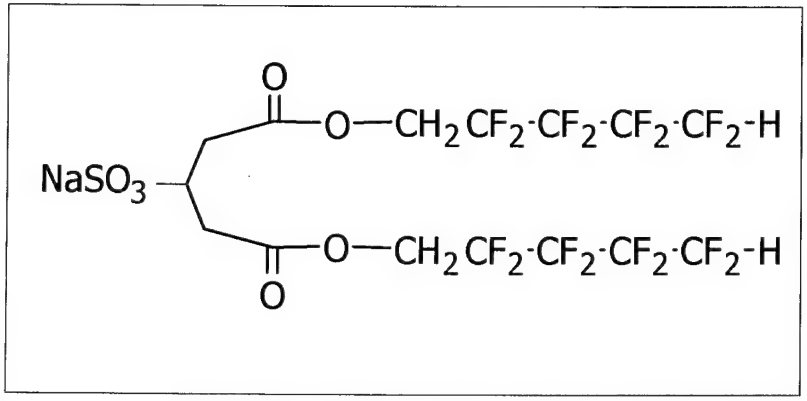


❷ fluoro-surfactants



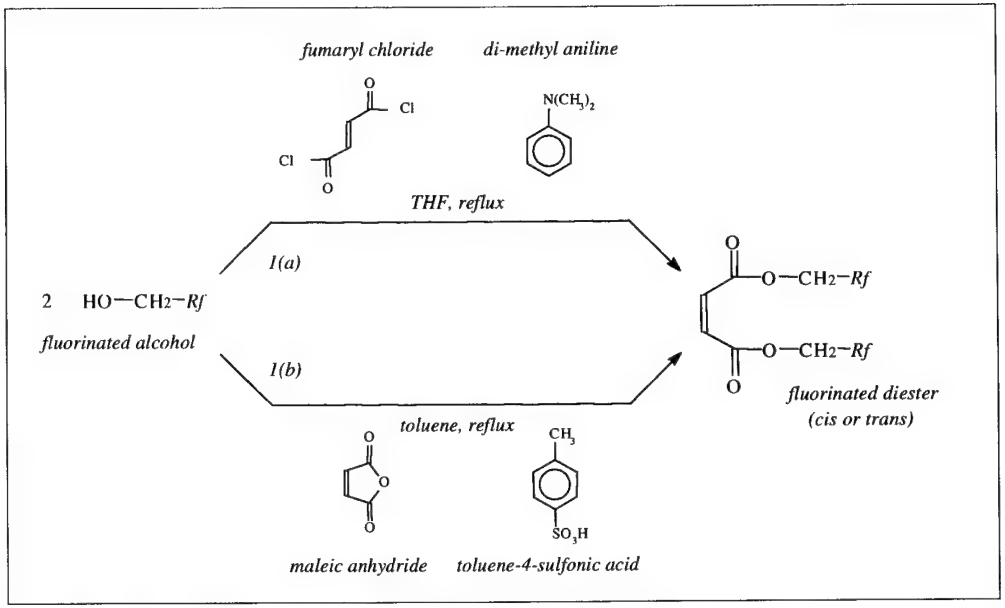
di-HCF4	n=1	m=4	X=H
di-HCF6	n=1	m=6	X=H
di-CF4	n=1	m=4	X=F

series 1	di-HCFm	n=1	m=2,4,6,8	X=H
series 2	di-CFm	n=1	m=2,3,4	X=F
series 3	di-CFmH	n=2	m=4,6	X=F

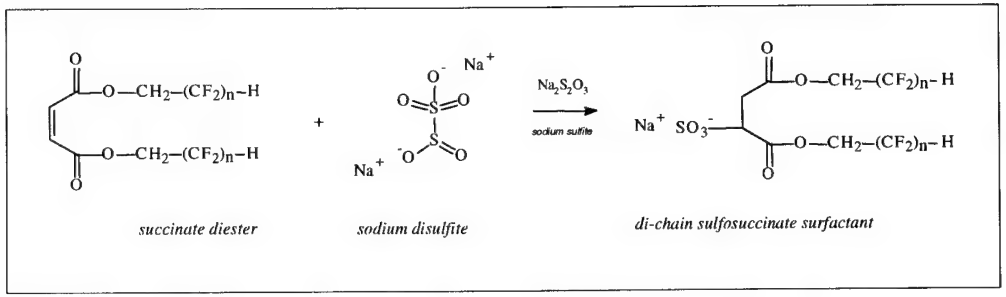


di-HCF4GLU

❷ surfactants

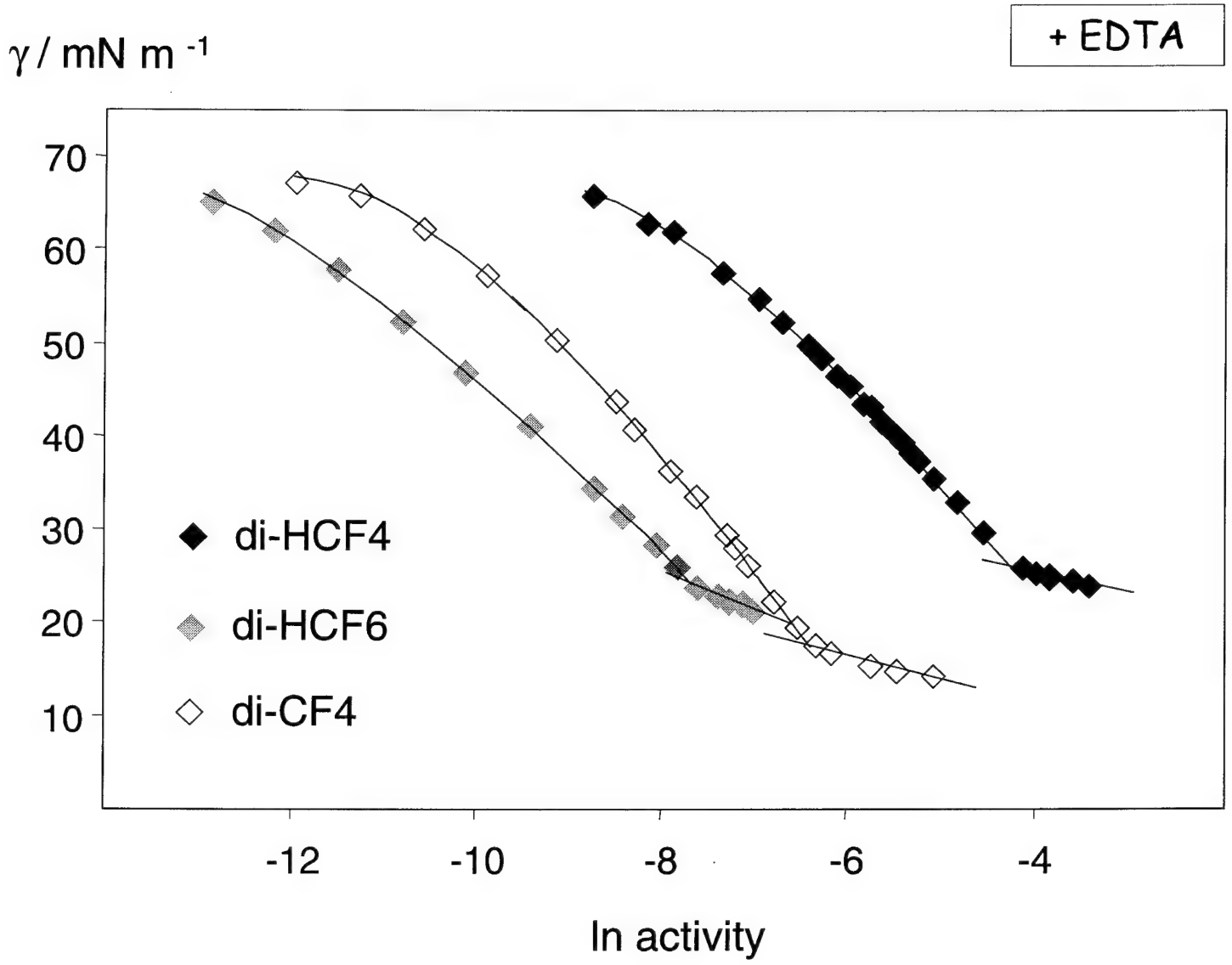


Reaction scheme 1 : synthesis of fluorinated diester

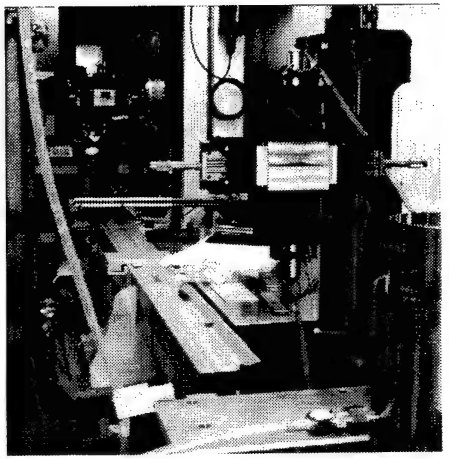


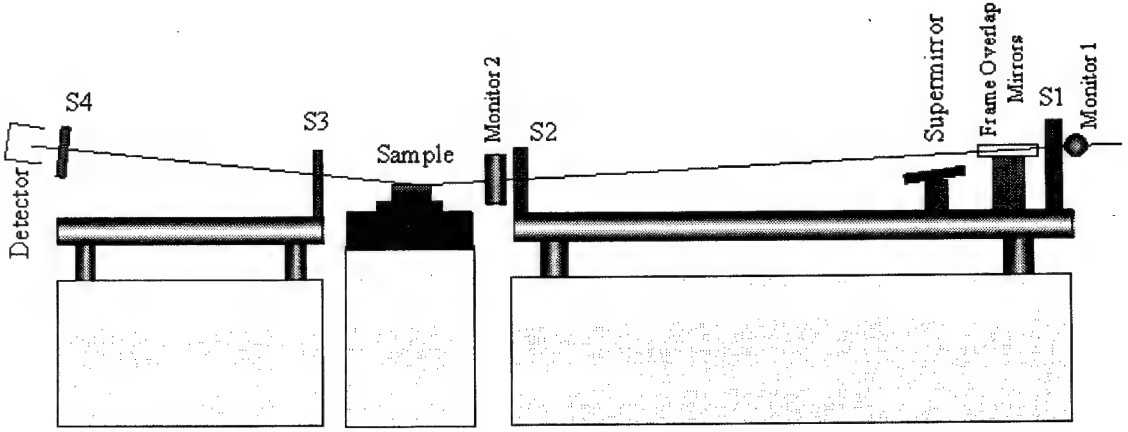
Reaction scheme 2 : sulfonation of diester to form surfactant

❸ aqueous phase behaviour

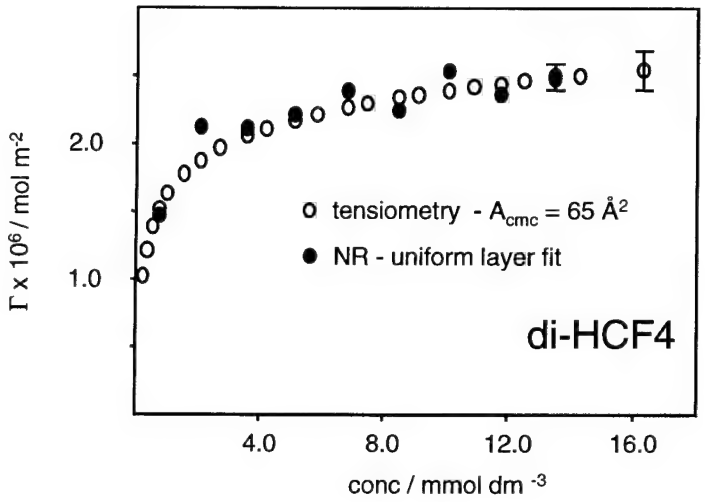


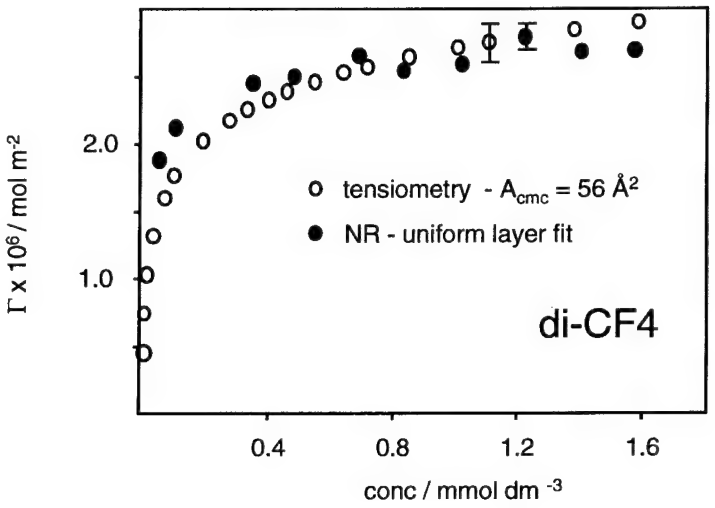
❸ aqueous behaviour - neutron reflection





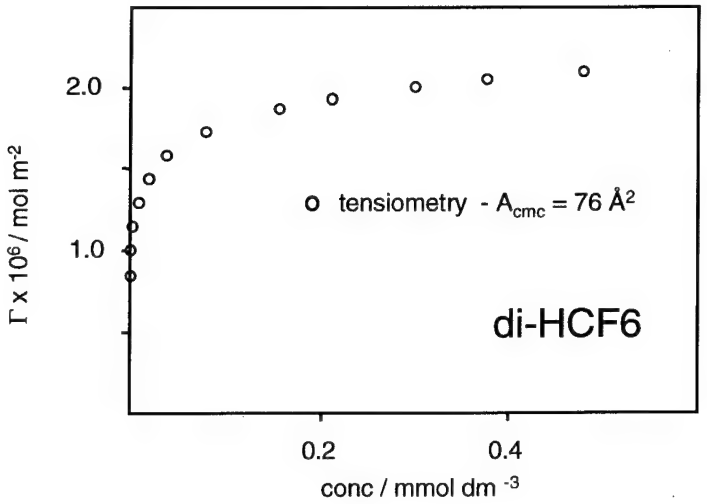
❸ aqueous phase behaviour



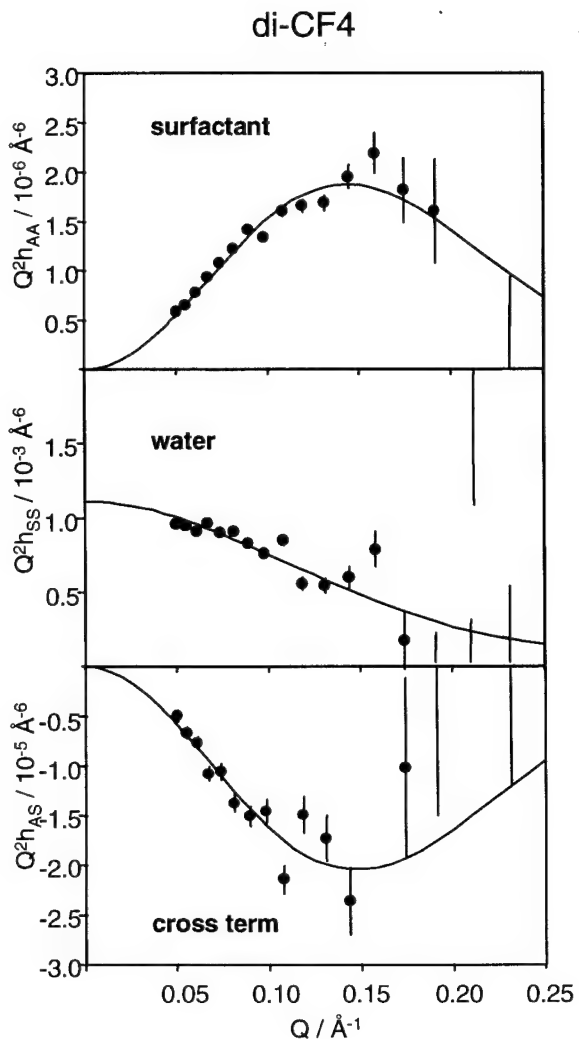


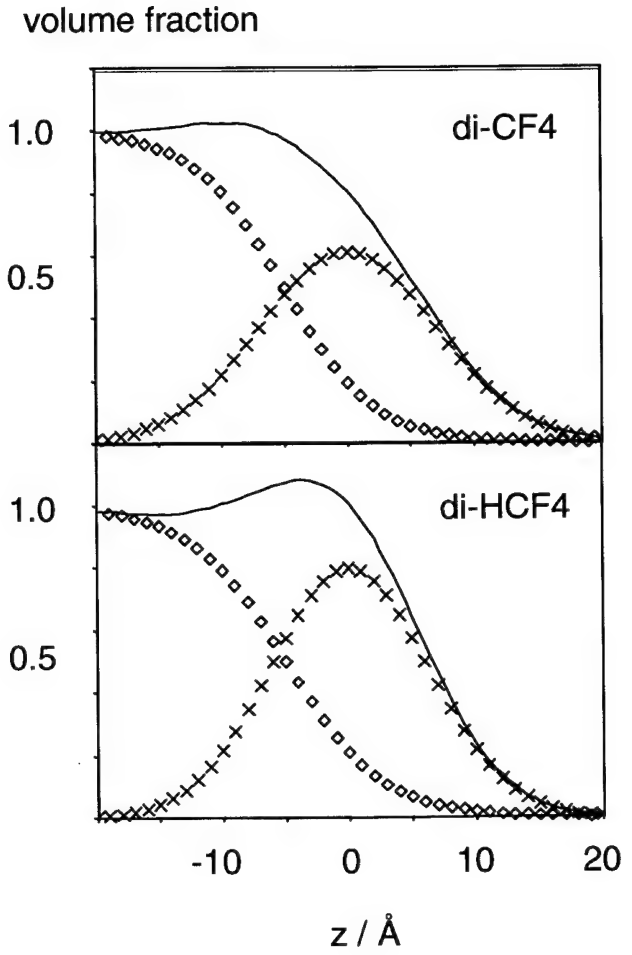
$$A = \frac{\sum b_i}{\rho\tau} = \frac{1}{\Gamma N_a}$$

$$\Gamma = -\frac{1}{2RT}\frac{d\gamma}{d\ln a}$$

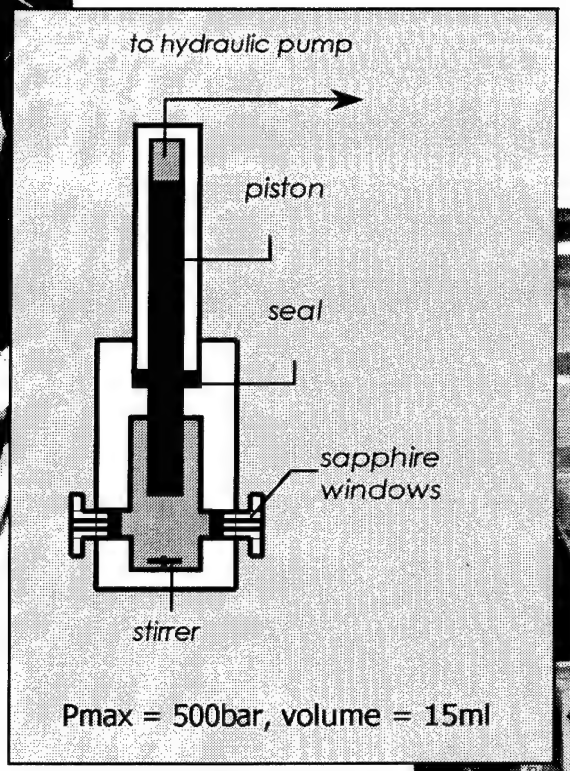


❸ aqueous phase behaviour
interfacial structure

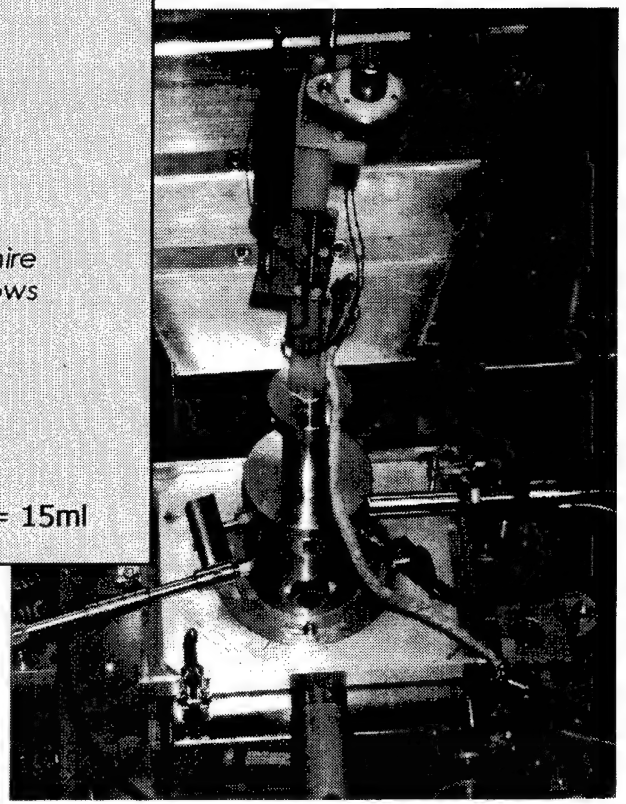




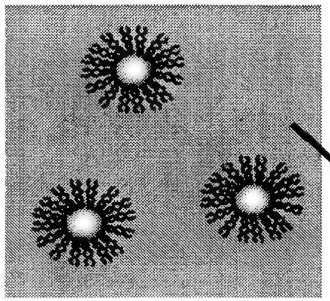
❹ water-in-CO_2 microemulsions

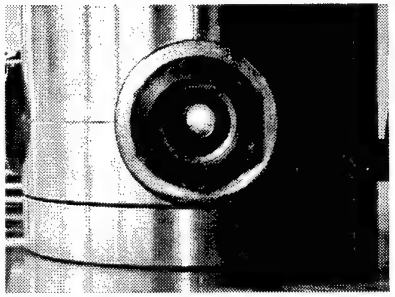


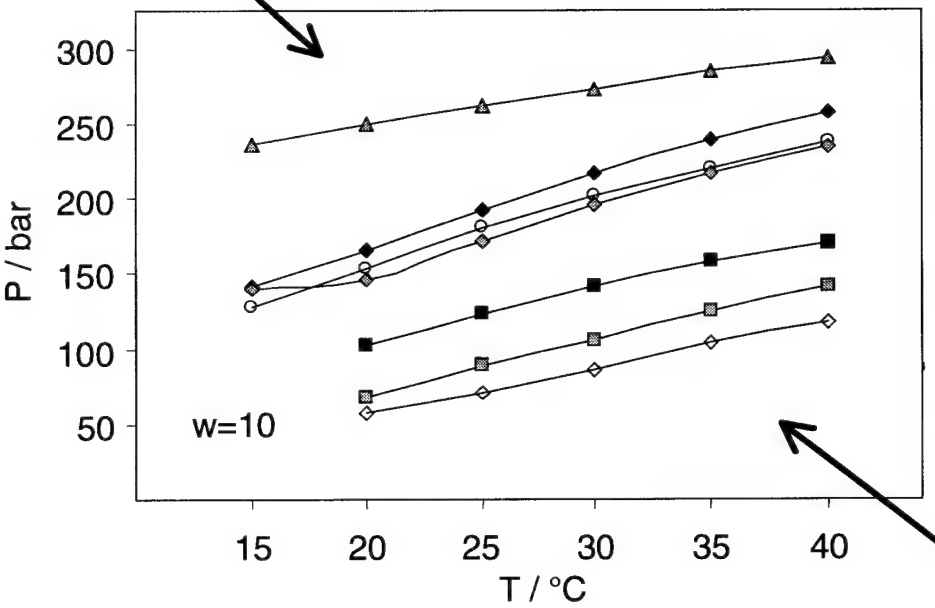
Pmax = 500bar, volume = 15ml

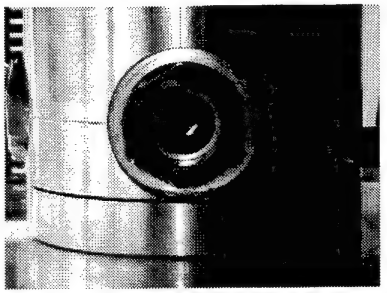


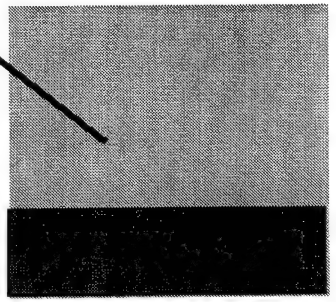
❹ water-in-CO_2 microemulsions



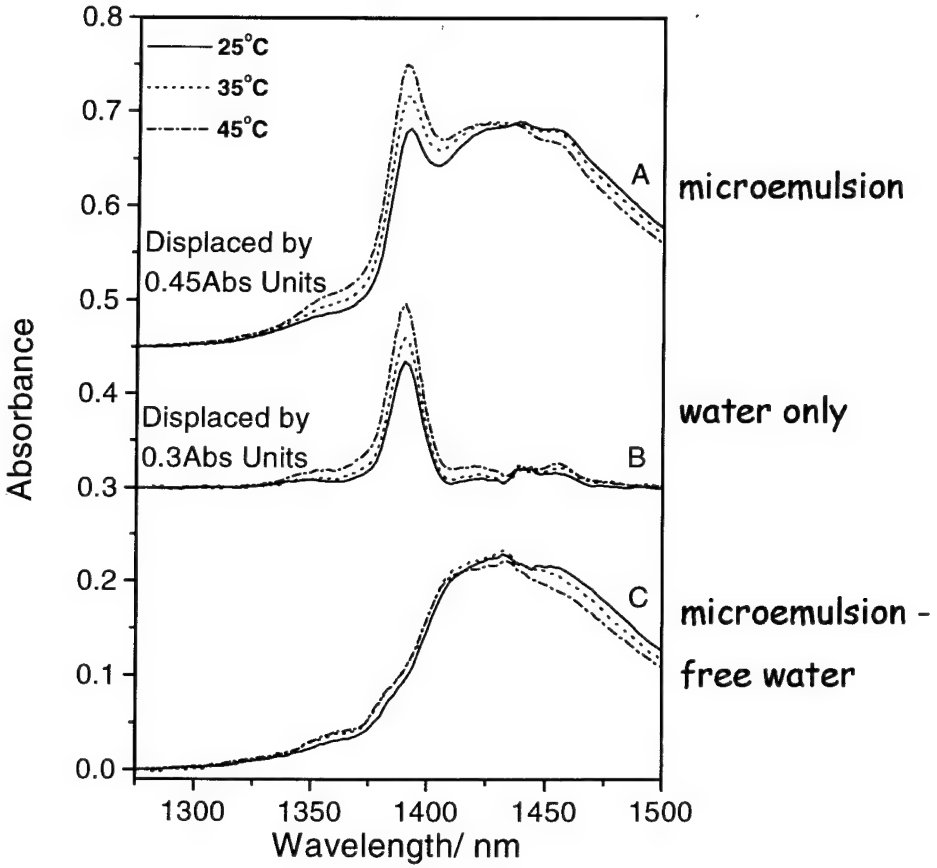


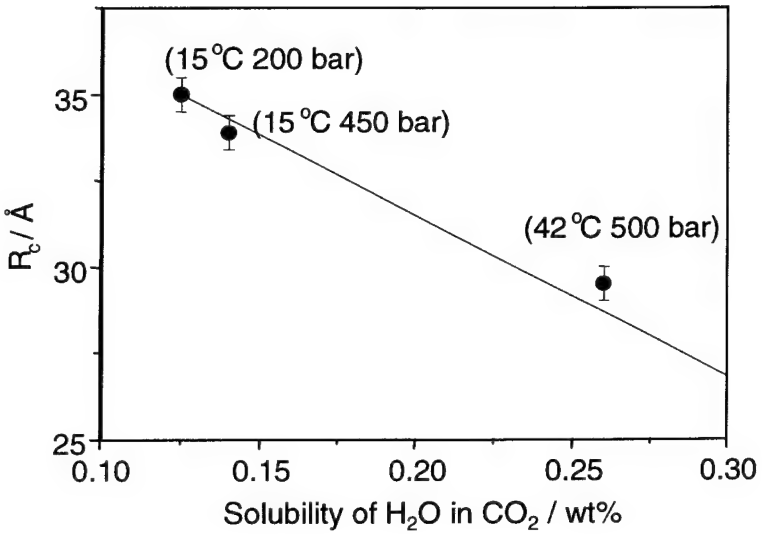




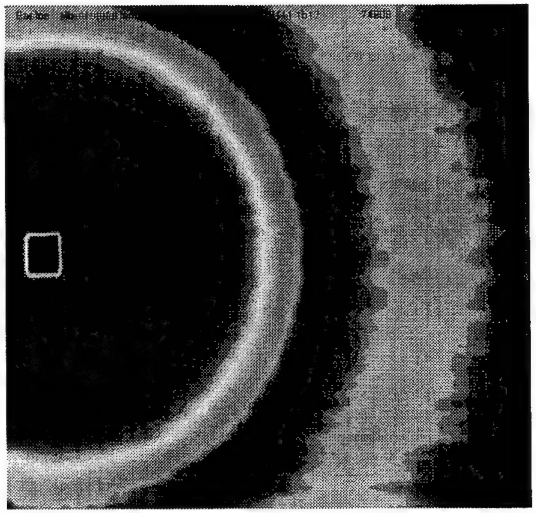


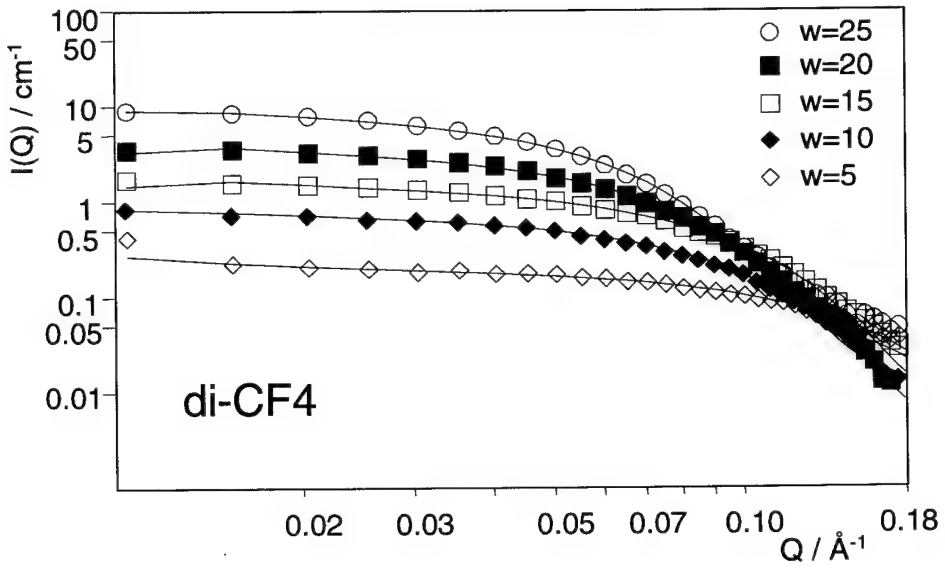
❹ water-in-CO_2 microemulsions





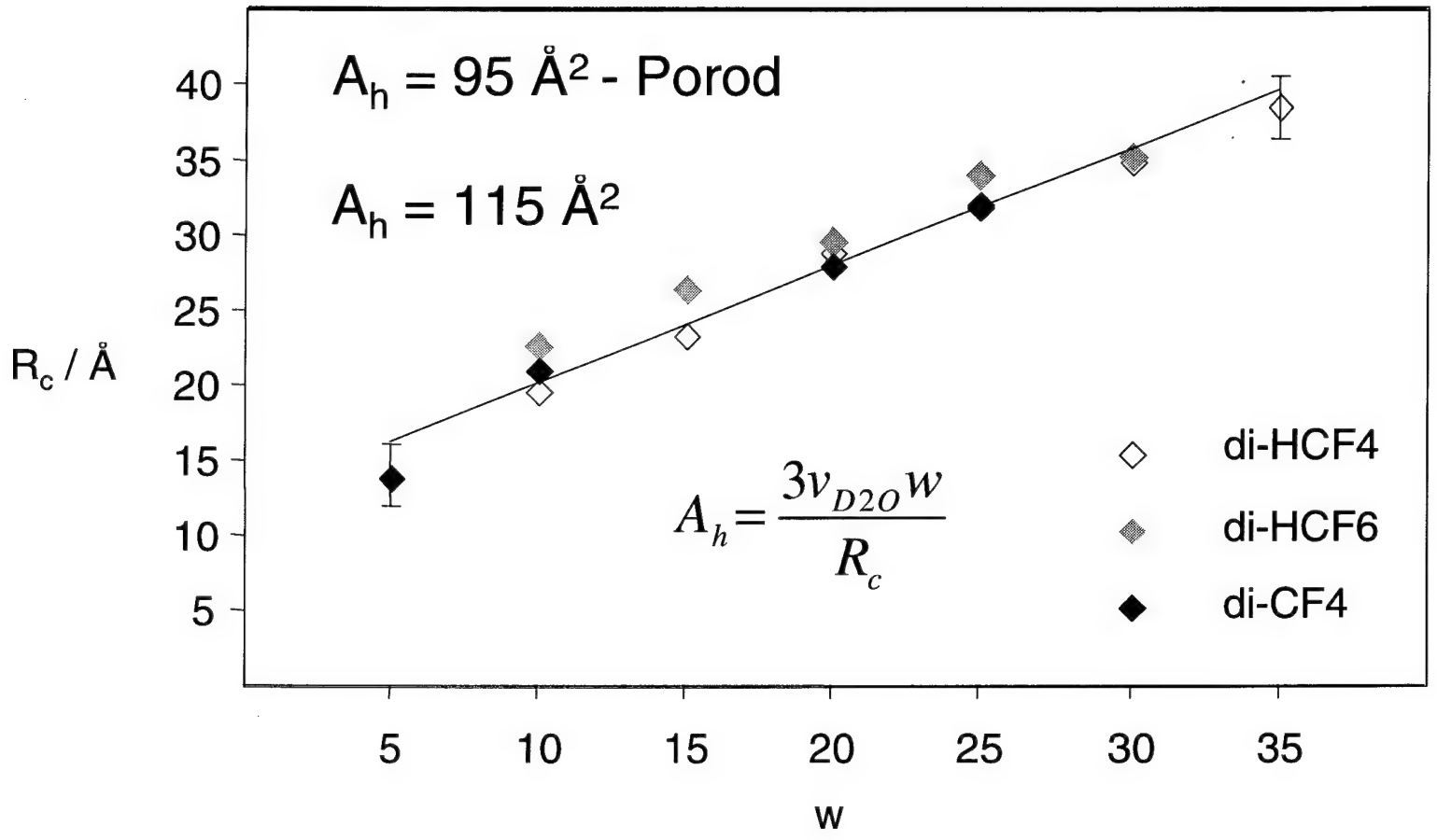
❹ water-in-CO_2 microemulsions





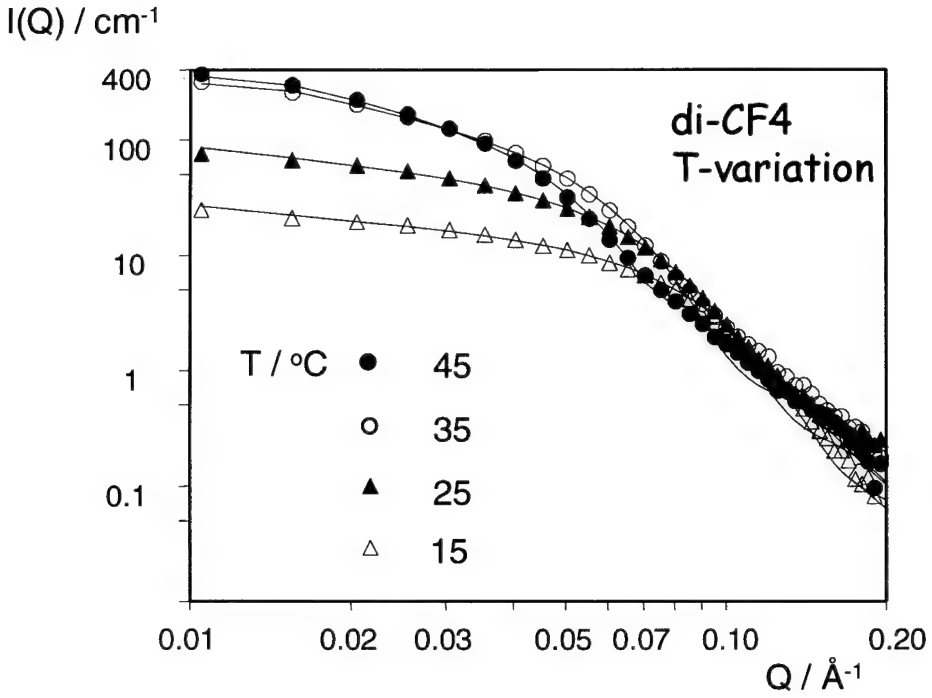
$I(Q) = A\,P(Q)\,S(Q)$

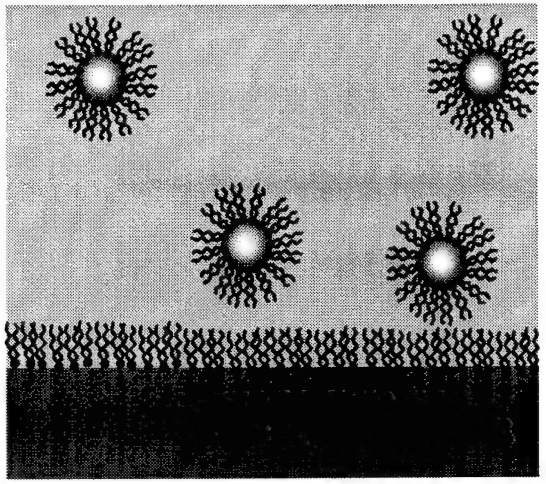
❹ water-in-CO_2 microemulsions

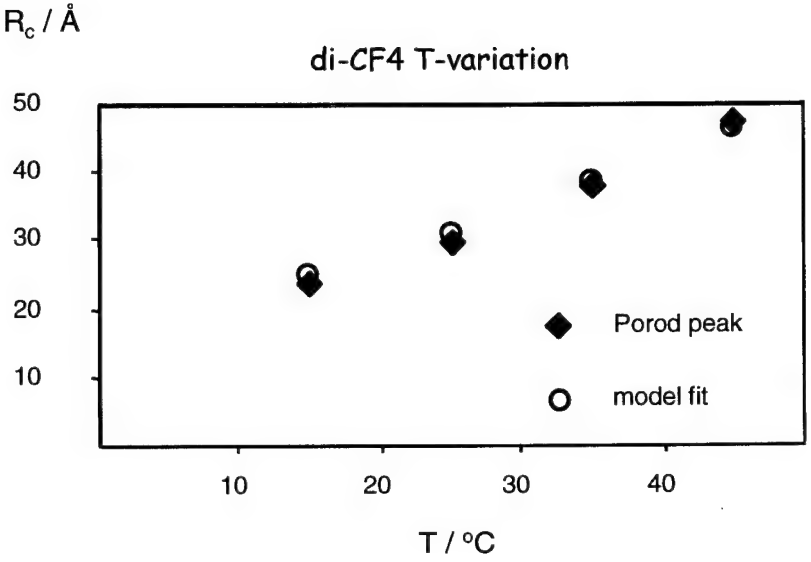


❹ water-in-CO_2 microemulsions

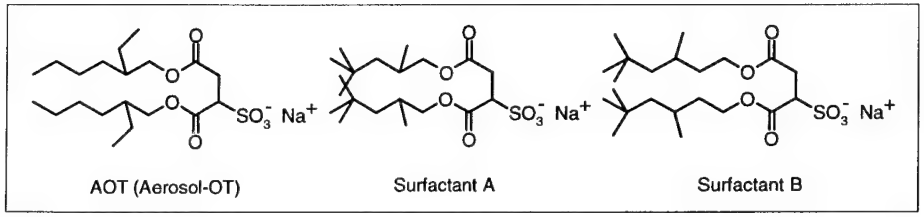
Winsor II phases

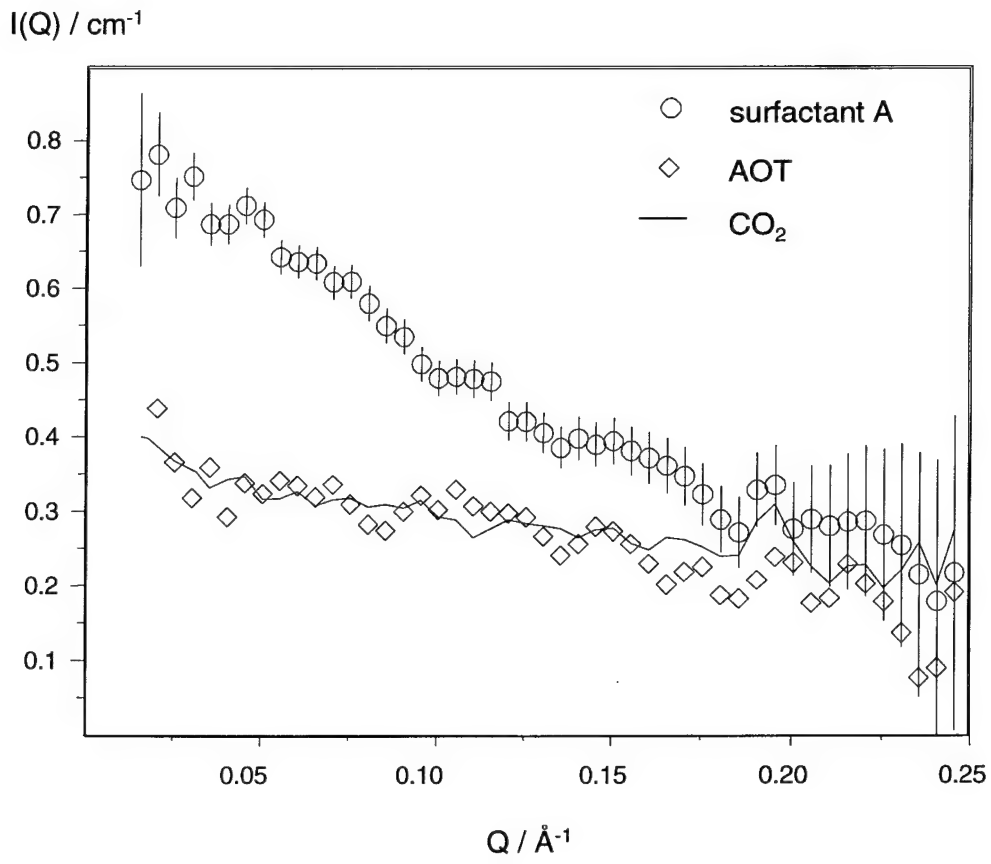




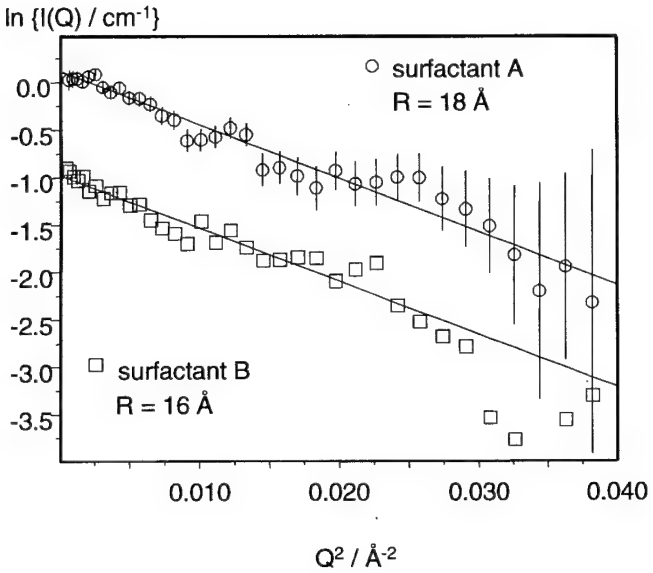


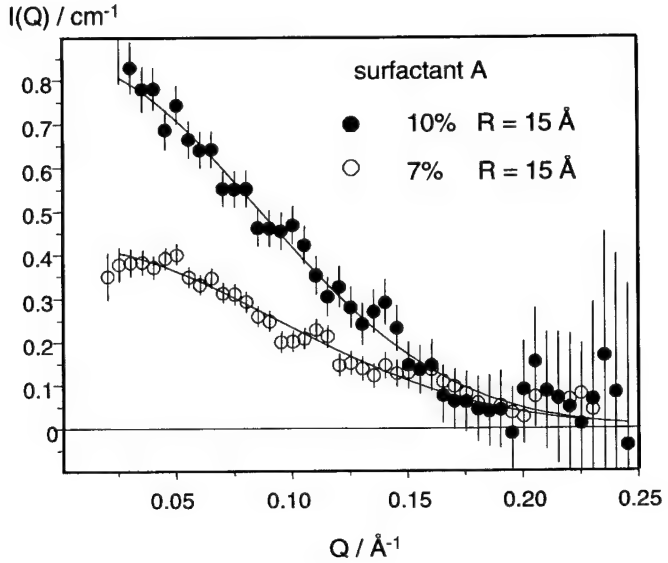
micelles of hydrocarbon surfactant in sc-CO_2

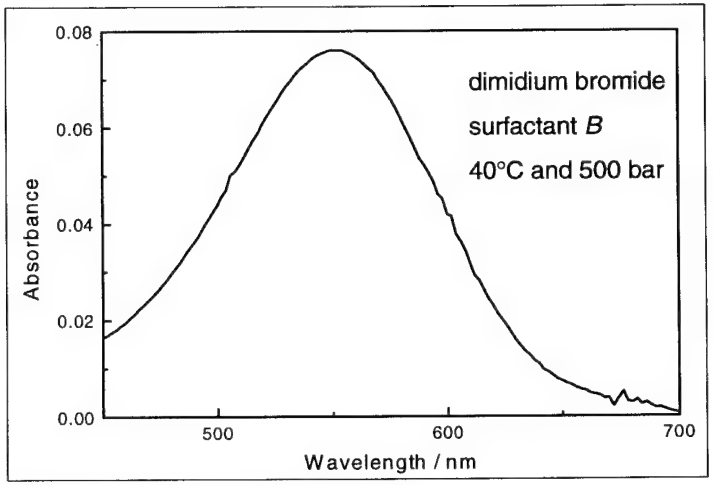




micelles of hydrocarbon surfactant in sc-CO_2







❺ conclusions

fluorinated sulfosuccinates :

- well characterised surfactants for water-in-CO_2 microemulsions
- phase stability and structure mirrors water-in-oils with hydrocarbon surfactants
- "optimum" tails $C_4F_9CH_2$- 10 x more expensive than H-$(CF_2)_4CH_2$-
- new cheap hydrocarbon systems mimic fluorocarbon behaviour in CO_2

	air-water	oil-water	CO_2-water
H-AOT	77 Å^2	76 Å^2	-
di-CF4 F-"AOT"	56 Å^2	-	110 Å^2

- less dense packing at CO_2-water interface c.f. oil-water

Enzymes in CO_2

David Steytler
Justin Holmes
Gareth Rees
Brian Robinson

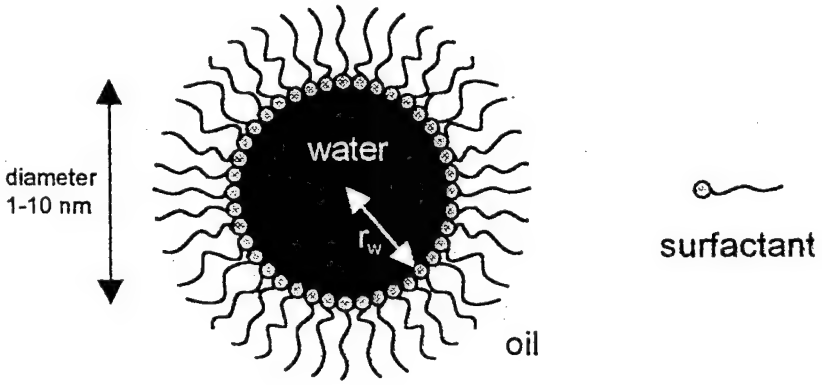
University of East Anglia

And

Julian Eastoe

University of Bristol

Microemulsions



- Thermodynamically stable
- Form spontaneously on shaking
- Optically transparent
- Droplet size, r_w depends on composition

$$r_w \approx \frac{3V_w}{A_s N_{AV}} \omega$$

V_w = molar volume of water

$\omega = [H_2O]/[Surfactant]_i$

A_s = Surface area of surfactant at w/s interface

$[Surfactant]_i$ = concentration of surfactant in system located at the interface

Enzymes are active in apolar organic solvents, when trace amounts of water are present.

Systems useful for synthesis of condensation products

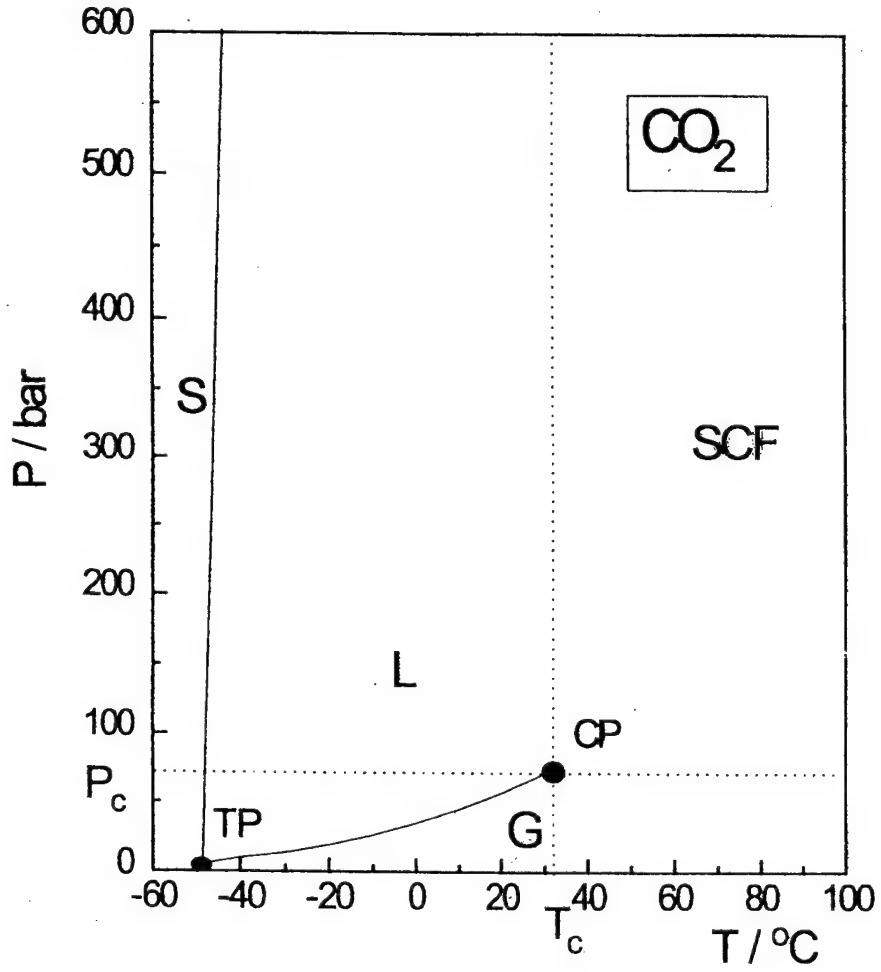
eg $RCOOH + RNH_2 \xrightarrow{E} RCONHR$

Microemulsions give more control over process, since small nanometer sized droplets are present

But organic solvents are inflammable and could be toxic.

Preferred media are H_2O and CO_2

CO_2: A Near-Critical Fluid (NCF)



- Above critical point CP (T_c = 31.1, °C P_c = 73.8 bar) single SuperCritical Fluid (SCF) phase exists

Physical Properties of NCF CO_2

- Wide range of density determined by P and T
- Continuous transition between liquid-like (high P) and gas-like (low P) properties

Solubility

- Low dielectric constant
- High solubility of Poly-dimethylsiloxane and fluorinated hydrocarbons

Transport Properties

- Low viscosity (0.07 cP * *cf.* hexane 0.3 cP)
- High diffusivity (~4 x10^{-8} m^2 s^{-1} * *cf.* hexane ~4 x10^{-9} m^2 s^{-1})

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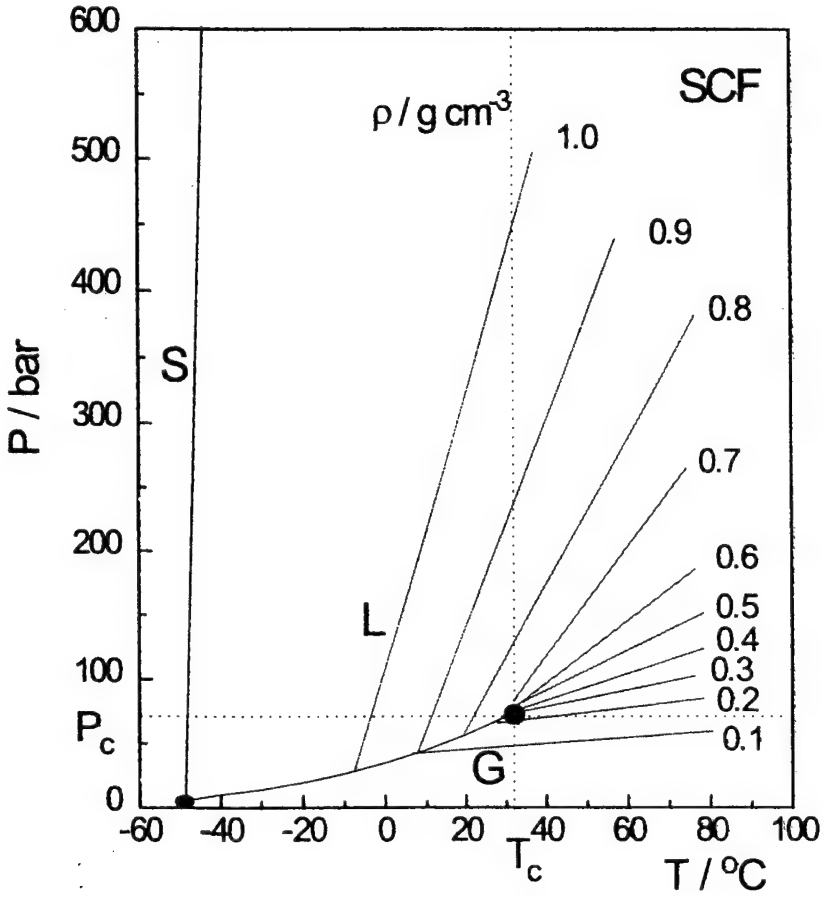
* for $\rho \sim$ 0.7 g cm^{-3}

CO_2: Density in the SCF Phase



- Wide range of density in SCF from gas-like (low P) to liquid like (high P)

To stabilise microemulsions in CO_2 use surfactant related to Na^+ AOT:

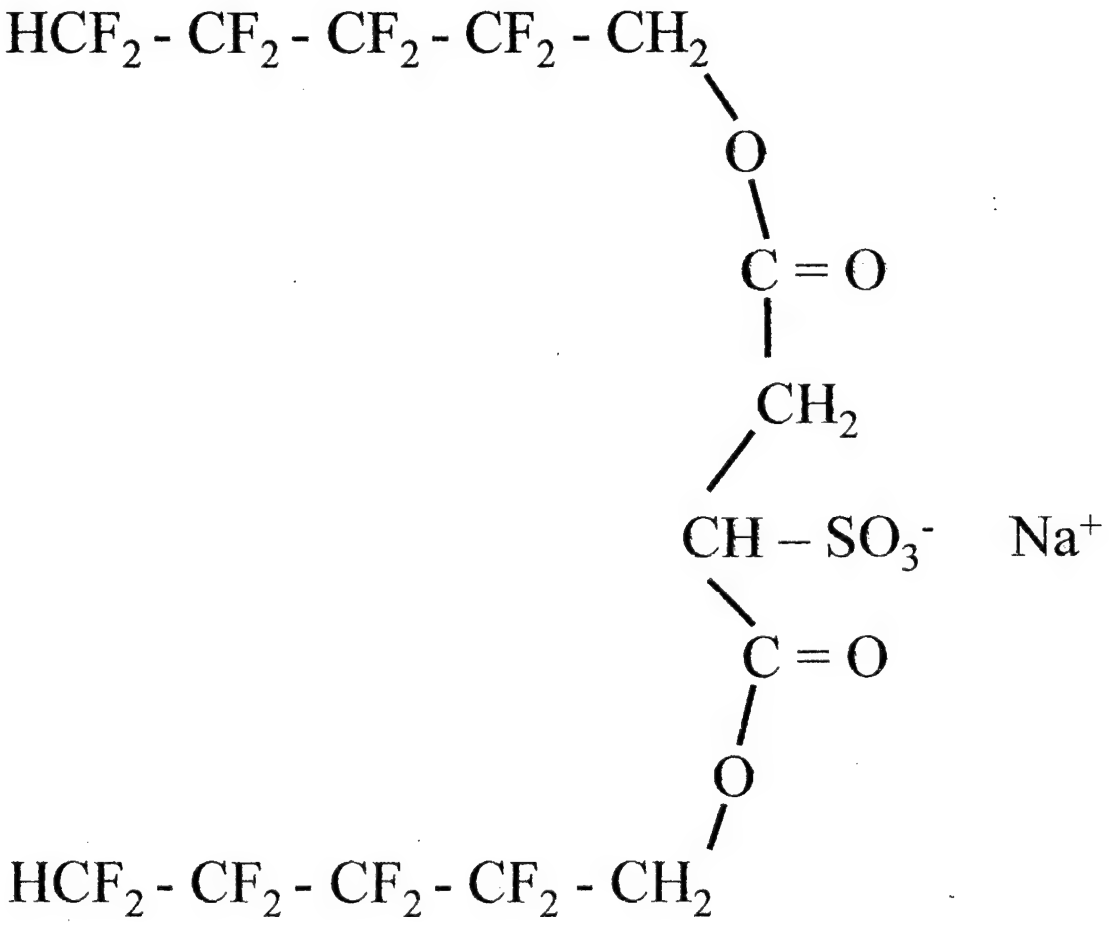
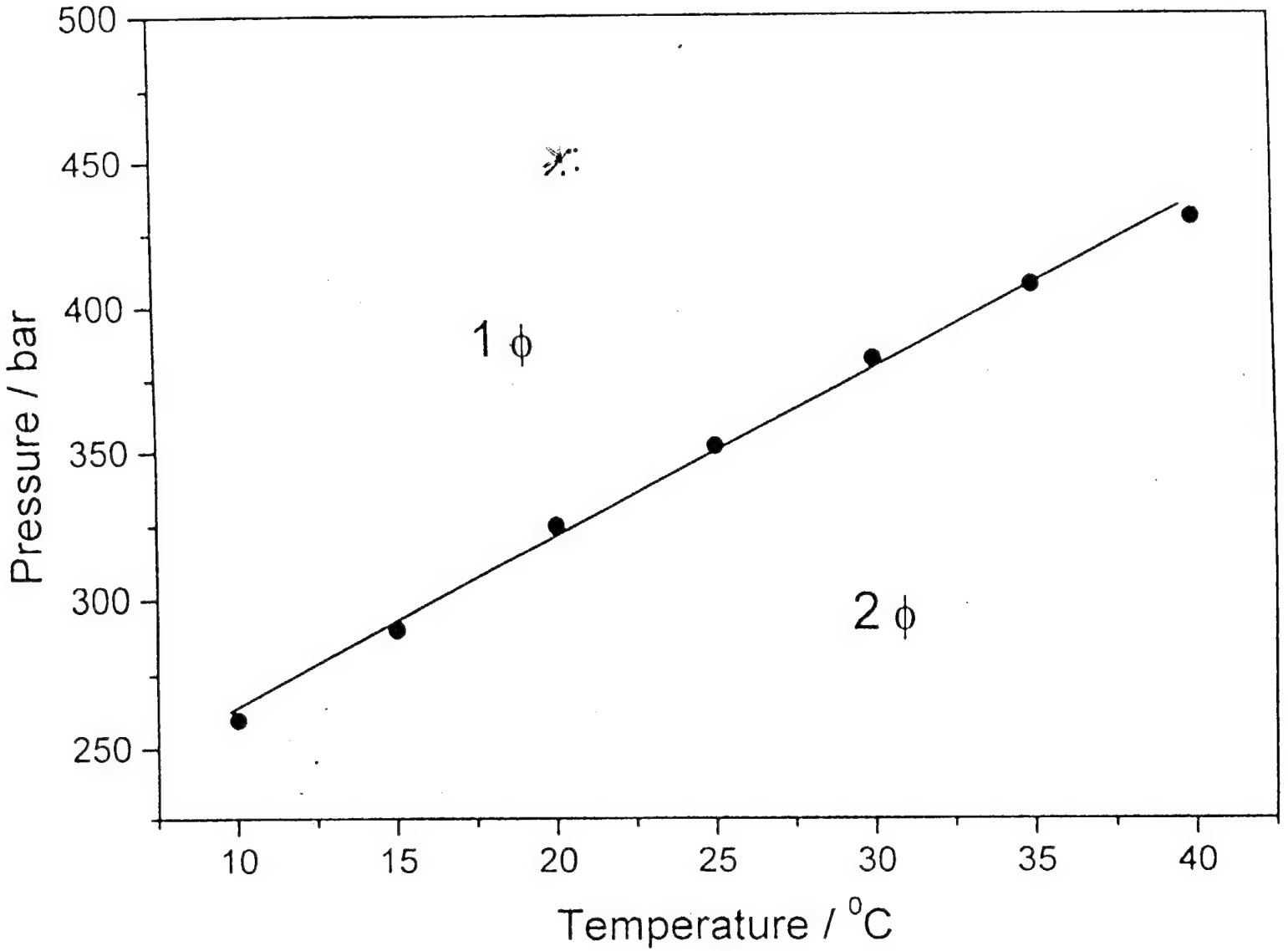


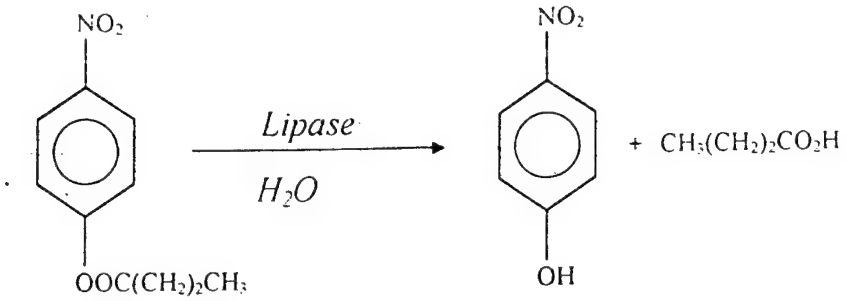
Figure 4 Steytler et al.



$W_0 = 10$; [surf] = 30mM pH = ~~7~~ (MES)

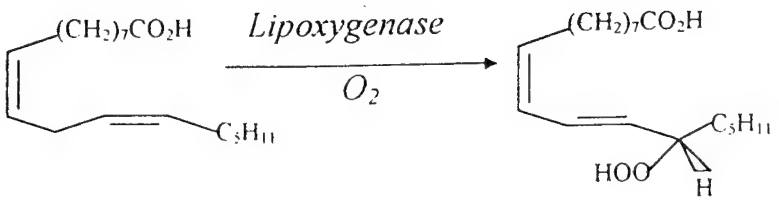
Figure 1

Scheme 1



p-Nitrophenyl butyrate *p*-Nitrophenol

Scheme 2



Linoleic Acid 13-hydroperoxyoctadecadienoic acid

Figure 5

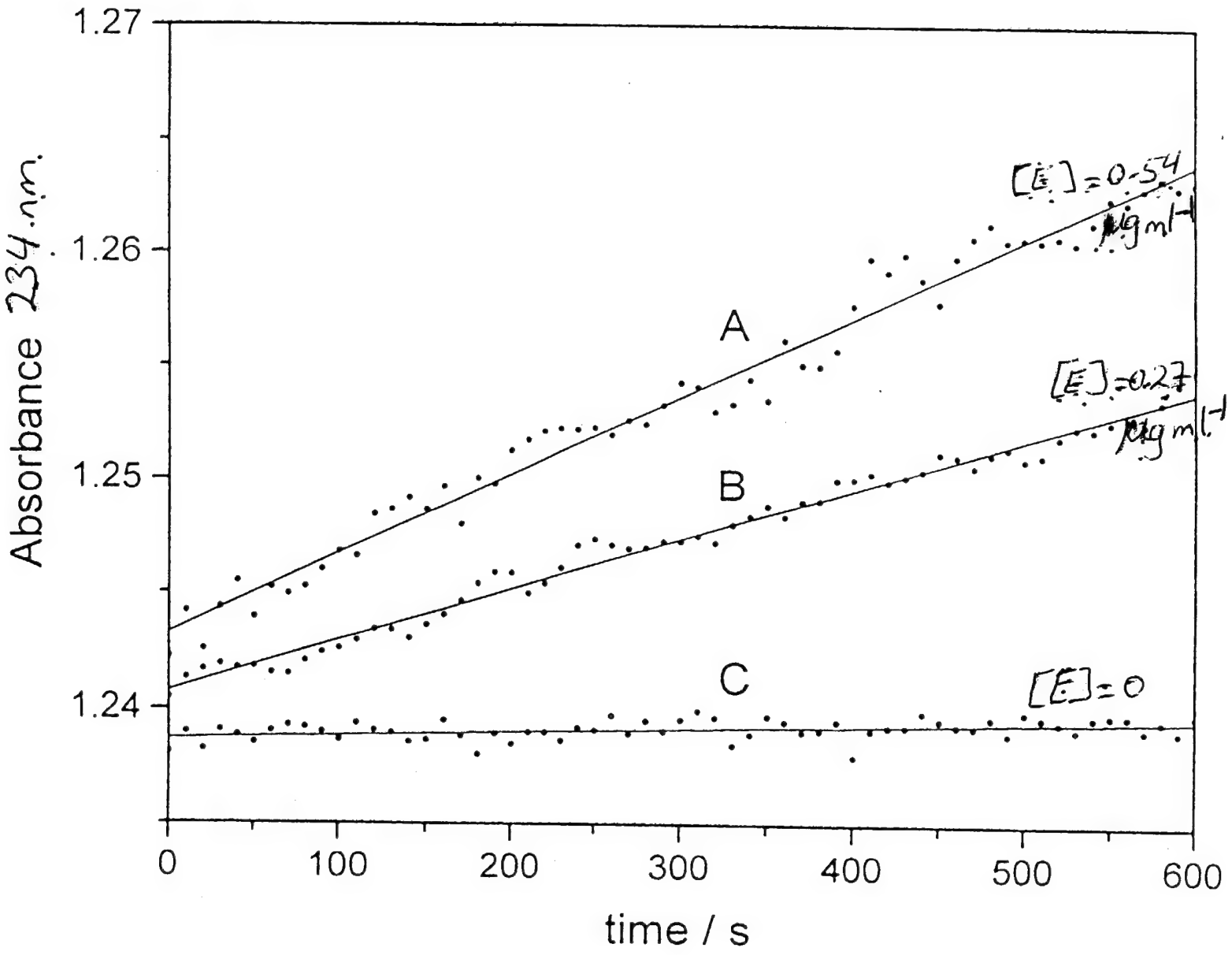

Absorbance 234 nm.
1.27
1.26
1.25
1.24
0
100
200
300
400
500
600
time / s
A
B
C
[E] = 0·54 μg ml⁻¹
[E] = 0·27 μg ml⁻¹
[E] = 0

Figure 4

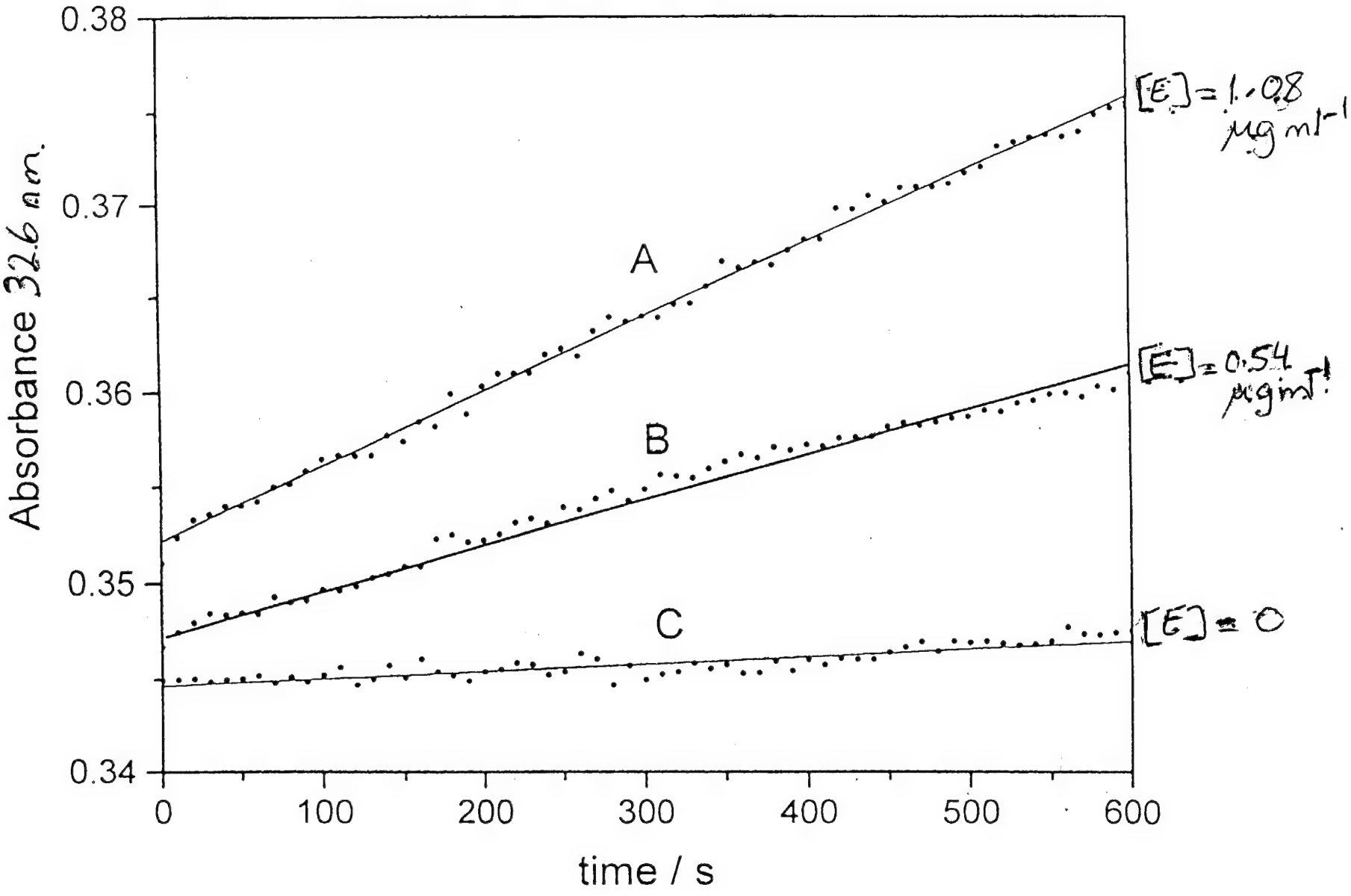
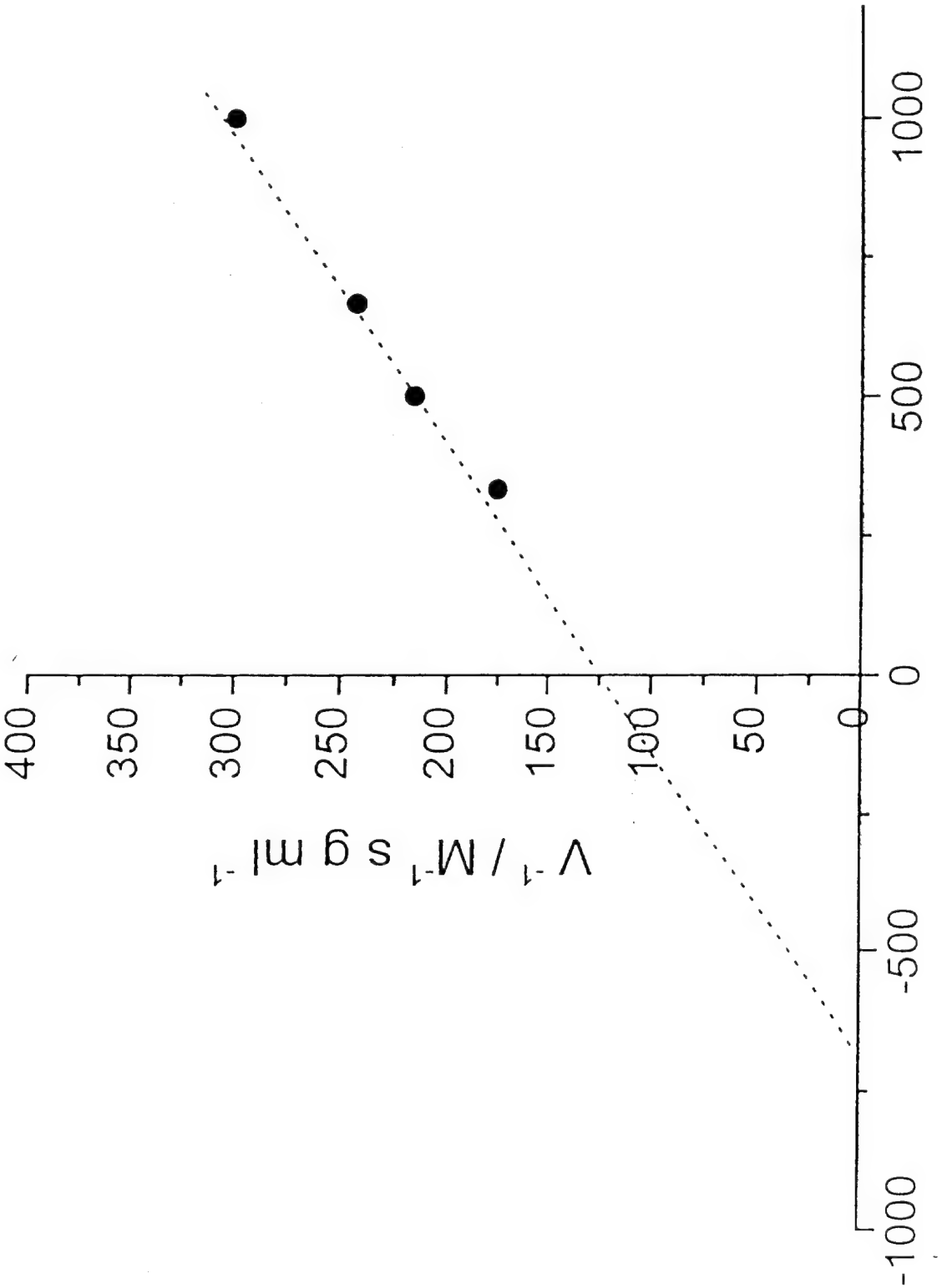

0.38
0.37
0.36
0.35
0.34
Absorbance 326 nm.
0
100
200
300
400
500
600
time / s
A
B
C
[E] = 1.08 μg ml-1
[E] = 0.54 μg ml-1
[E] = 0

Figure 6


400
350
300
250
200
150
100
50
0
-1000
-500
0
500
1000
v^{-1} / M^{-1} s g ml $^{-1}$
$[S]_T^{-1}$ / M^{-1}

CONCLUSIONS

1. Water droplets stabilised in CO_2 using diHCF_4.
2. CV lipase and soybean lipoxygenase are active in this solvent system.
3. Rates are similar to those in AOT microemulsions in heptane.

References:

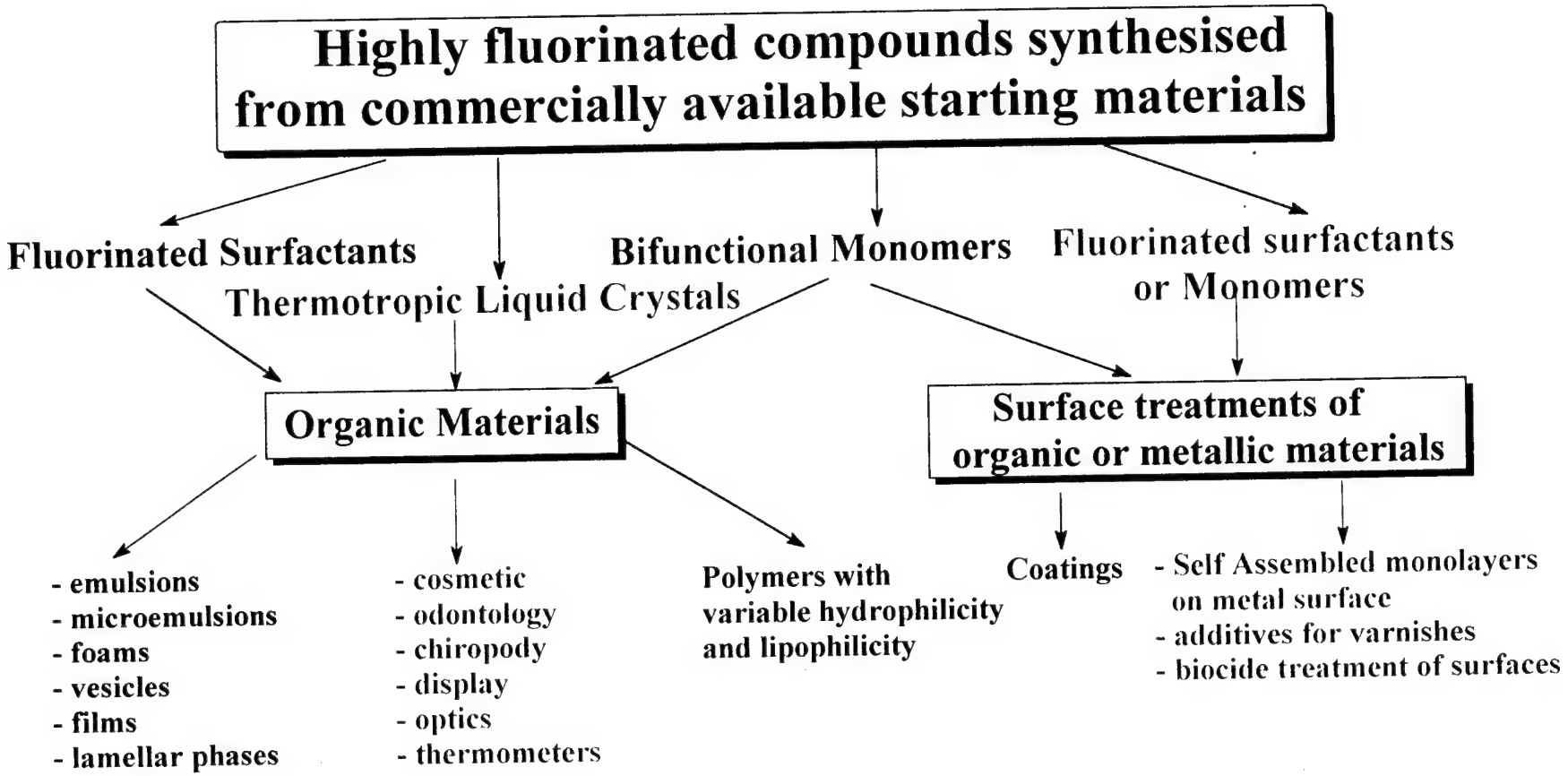
1. Eastoe J, Bayazit Z, Martel S, Steytler DC, Heenan RK, Langmuir 1996, 12, 1423.
2. Holmes JD, Steytler DC, Rees GD, Robinson BH, Langmuir 1998, 14, 6371

FLUORINE CHEMISTRY AT THE UNIVERSITY OF NICE-SOPHIA ANTIPOLIS:

Highly Fluorinated Compounds for Molecular Organised Systems

Frédéric Guittard, Serge Géribaldi.

Chimie des Matériaux Organiques et Métalliques (CMOM), Université de Nice-Sophia-Antipolis, Parc Valrose, 06108, Nice Cedex-2, France


Highly fluorinated compounds synthesised from commercially available starting materials
Fluorinated Surfactants
Thermotropic Liquid Crystals
Bifunctional Monomers
Fluorinated surfactants or Monomers
Organic Materials
Surface treatments of organic or metallic materials
- emulsions
- microemulsions
- foams
- vesicles
- films
- lamellar phases
- cosmetic
- odontology
- chiropody
- display
- optics
- thermometers
Polymers with variable hydrophilicity and lipophilicity
Coatings
- Self Assembled monolayers on metal surface
- additives for varnishes
- biocide treatment of surfaces

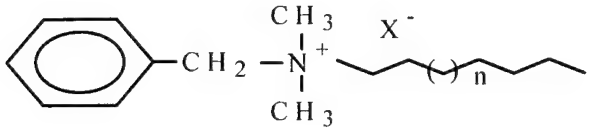
Recent Advances in Fluorinated Surfactants

DEVELOPMENT OF HIGHLY FLUORINATED BISAMMONIUMS AND EVALUATION OF THEIR BIOCIDE PROPERTIES

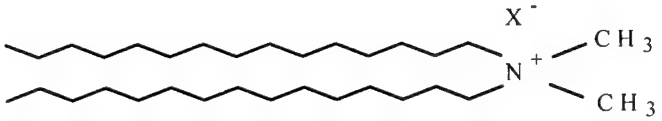
BIOCIDE QUATERNARY AMMONIUMS

✓Historic:
- ⇨Discovery by *Jacobs and Heidelberger* (1915)
- ⇨Biocide quaternary ammonium surfactants: *Dogmagk* (1935).

✓Commercially available compounds (examples):

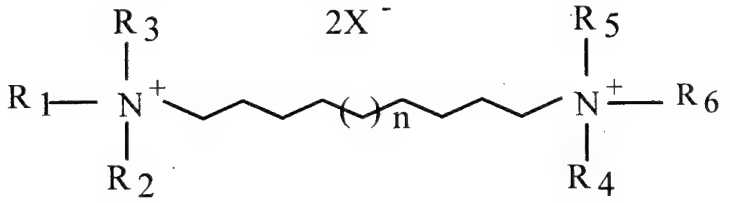


BTC 824, 835, 50 USP (Stepan onyx)
BARQUAT MB 50 (Lonza)



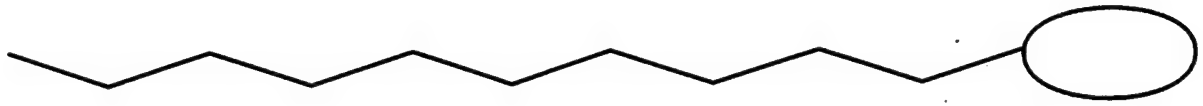
BARDAC 2050, 205M, 2250 (Lonza)

✓ Number of other works especially :

bis-quaternary ammonium salts	

BIOLOGICAL ACTIVITY = f (SURFACTANT PROPERTIES)

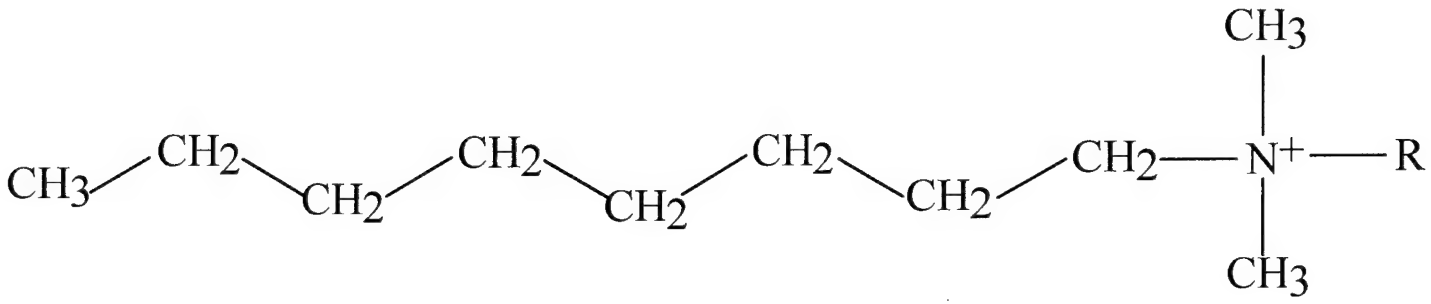
Surfactant ⇨



Non-polar tail

Polar head

Commercial example : Bardac



MICROBIOLOGICAL TESTS

- Synthesis of four series of molecules (**Quaterfluo™**) noted : Ax, Bx, Cx and Dx.
- Measurement of their Minimal Inhibitory Concentration (MIC).

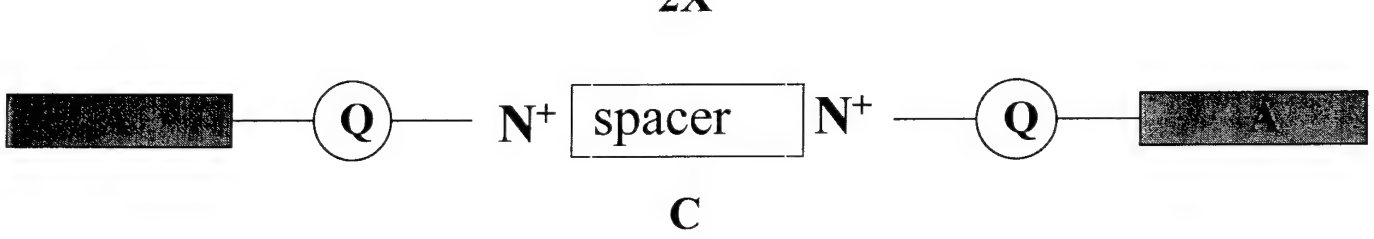
Selected Microorganisms:

- Bacterias
  - ***Pseudomonas Aeruginosa (Gram-)***
  - ***Staphilococcus Aureus (Gram+)***
- Fungis
  - ***Candida Albicans***
  - ***Aspergillus Niger***

HIGHLY FLUORINATED SURFACTANTS : OUR WORK

- Synthesis and characterisation
- Evaluation of anti-bacterial and anti-fungal properties (MIC)

- General structure inverstigated (named **Quaterfluo™**):

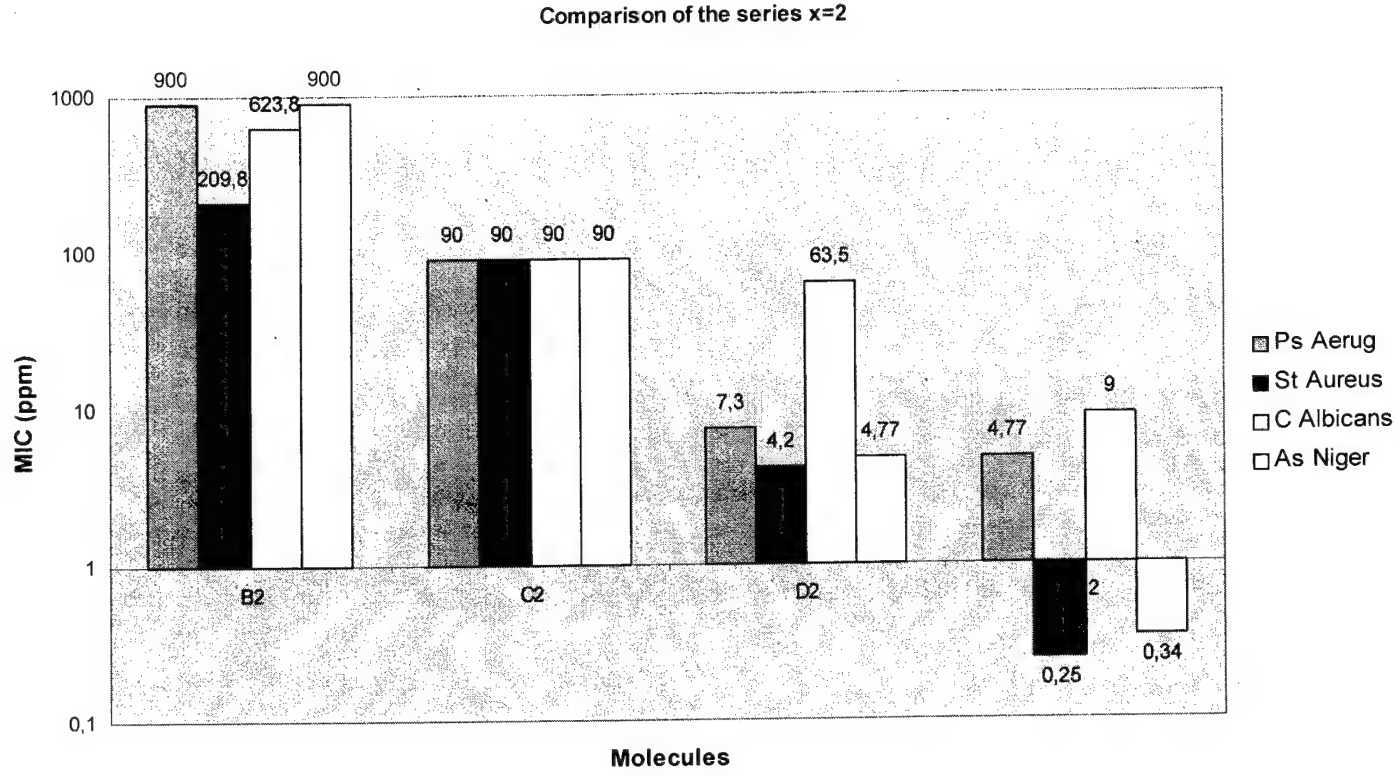


- A=Perfluorinated chain
- Q=Connector (chemical function)
- C=Spacer
- N=Nitrogen atom
- X=Counter-ion Br or Cl

RESULTS (1)

MIC measurements from A2,B2,C2 and D2.

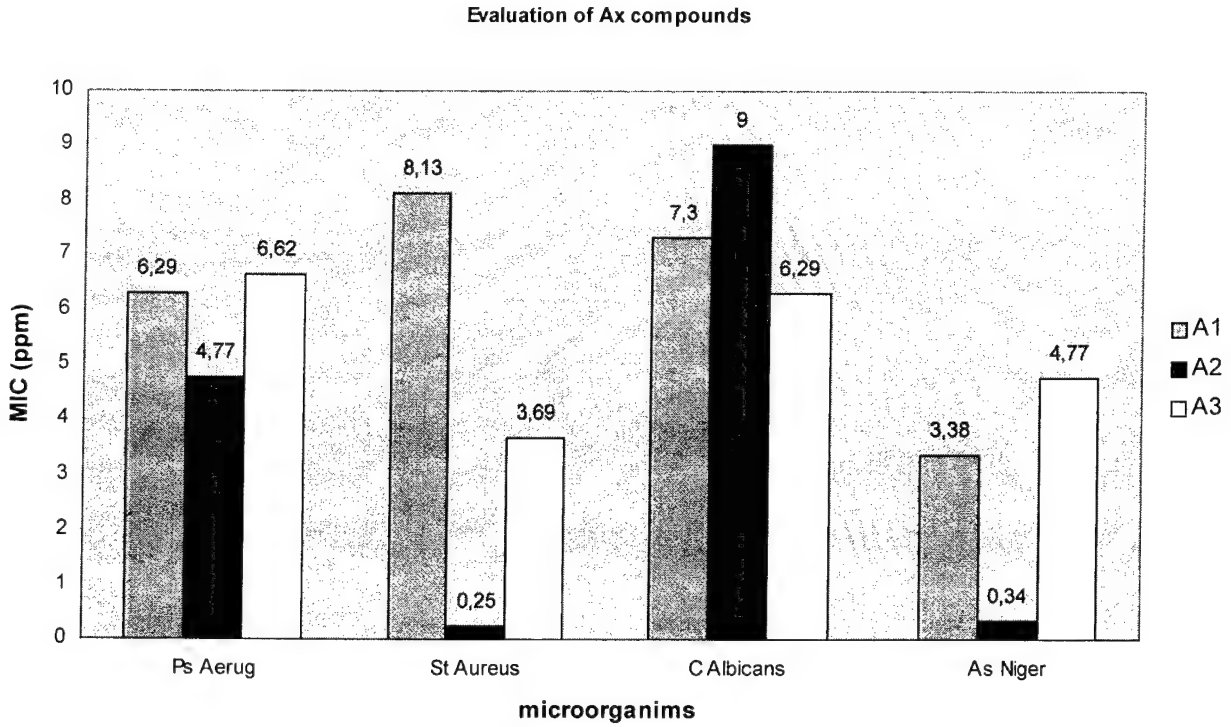
Figure 1 : Comparison of biocidal activities of series noted x=2



RESULTS (2)

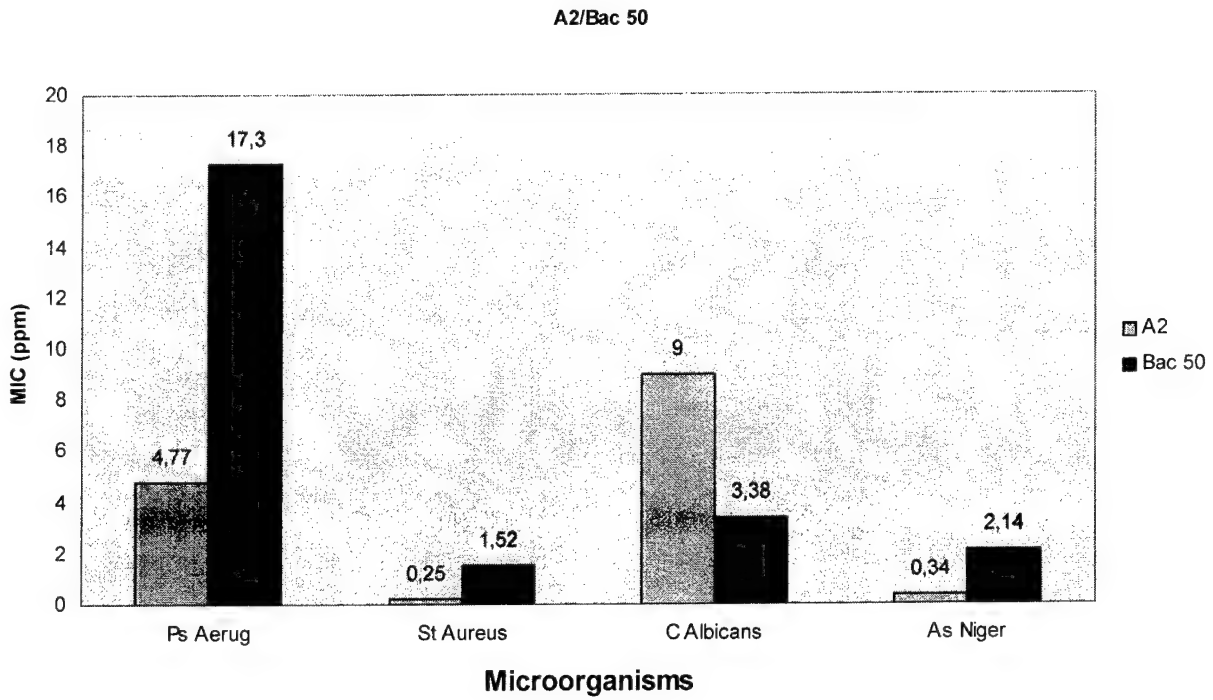
MIC Measurements from A1, A2, A3.

Figure 2 : Comparison of biocidal activities of series Ax =f(microorganisms)



RESULTS (3)

Figure 3 : Comparison of the biocidal activities of BAC 50 and A2



PRELIMINARY CONCLUSIONS

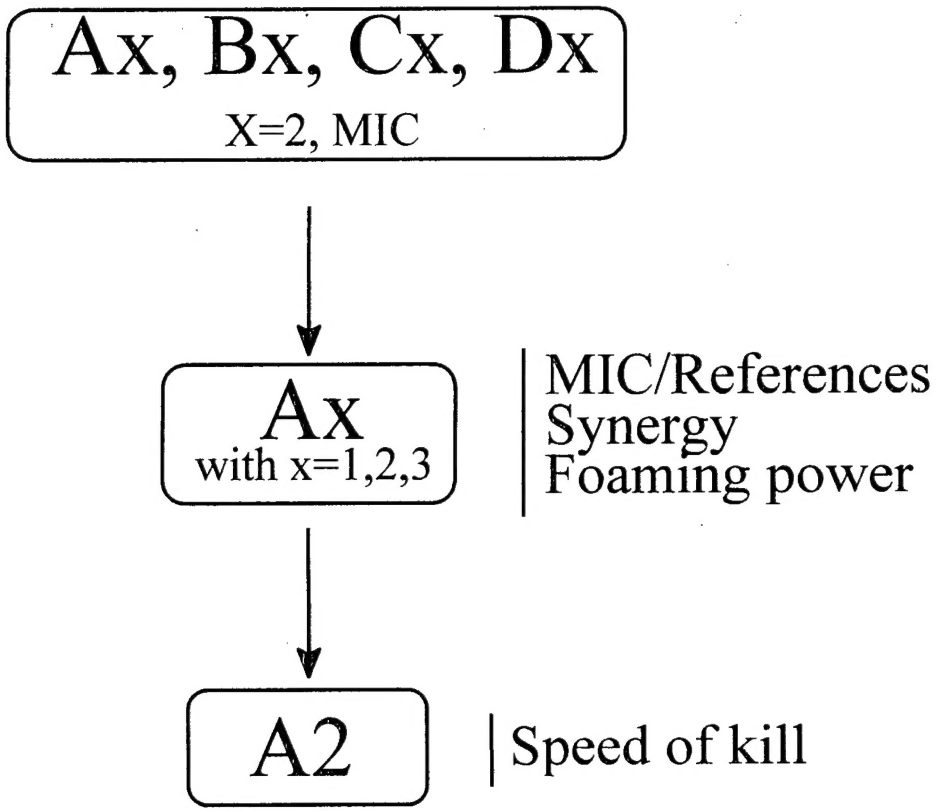
- MIC Results
  - All are biocides
  - Specificity of action
  - Performances / ref.
- Other experiment carried out from these compounds :

1. Foaming power study
2. Speed Of Kill (SOK) test

EVALUATION OF THE FOAMING POWER OF COMPOUND Ax
RESULTS FROM RUNNING WATER

—— results for A2 (for example)

Cpds used	Temp (°C)	water	conc(ppm)	Formation time(s)	High (cm)	Foam Stability
Bac 50	20	B	5	>120	6	low
A2	20	B	5	22	31	high
Bac 50	20	B	100	25	23	average
A2	20	B	100	20	29	high
Bac 50	45	B	5	> 240	5	low
A2	45	B	5	22	31	high
Bac 50	45	B	100	26	21	low
A2	45	B	100	16	29	high



PERSPECTIVES

- ✓These first results are interesting : high biocide activities
- ✓Exploration of biocides properties of highly fluorinated quaternary ammoniums
- ✓Determination of the critical parameters